CORRIGENDUM

1. Page 2, Line 20: eicosapentaenoic (not eicosapetanenoic).
2. Page 4, Line 15: histidine (not histadine).
3. Page 23, Line 11: ...through hydroxy-directed processes (delete the word an).
4. Page 46 and Page 137: The correct ^{13}C NMR spectral data for compound **87** are as follows: (75 MHz, $CDCl_3$) 200.8, 170.7, 52.5, 41.1, 36.3, 30.2, 28.5, 15.2.
5. Page 52, Line 1: preceding (not preceeding).
6. Page 64, Line 11: *tert*-butyllithium (not *tert*-butylithium).
7. Page 67, Line 16: its (not it).
8. Page 85, Line 24: Hunsdiecker (no Umlaut).
9. Page 90, Line 25: adsorbent (not adsorbant).
10. Page 95, Line 22: congener (not congenor).
11. Page 108, Line 3: phosphorus (not phosphorous).
12. Page 174, Line 1: The correct name for compound **205** is **(3a*S*, 5a*R*, 6a*R*, 6b*S*)-6,6-Dichloro-4-iodo-2,2-dimethyl-5a,6,6a,6b-tetrahydro 3a*H*-cyclopropa[*e*]-1,3-benzodioxole.**
13. Page 183, Line 6: The correct name for compound **216** is **(3a*S*, 5a*R*, 6a*R*, 6b*S*)-6,6-Dichloro-4-iodo-2,2,6a-trimethyl-5a,6,6a,6b-tetra hydro-3a*H*-cyclopropa[*e*]-1,3-benzodioxole.**
14. The references listed below need to replace those of the same number and which appear in the body of the thesis:

24. Ichichara, A.; Shiraishi, K.; Sato, H.; Sakamura, S.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.
38. Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.
46. Gibson, D. T.; Subramanian, V. in *Microbial Degradation of Organic Compounds,* Gibson, D. T., Ed; Microbiology Series, Vol. 13, Marcel Dekker: New York, 1984; Chapter 7.
94. Kleschick, W. A.; Reed, M. W.; Bordner, J. *J. Org. Chem.* **1987**, *51*, 3168.
104. (a) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1989**, *45*, 3039.
148. Horner, L.; Hoffman, H.; Wippel, H. G. *Chem Ber.* **1958**, *91*, 61.
162. Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863.
176. Wender, P. A.; Seiburth, S. McN.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

CHEMOENZYMATIC ROUTES TO ENANTIOPURE CYCLOPROPANES

A thesis submitted for the degree of Doctor of Philosophy
of The Australian National University

by

Grant Forman

Research School of Chemistry
Canberra, Australia

November, 1998

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by myself during the period 1995-1998 and has not been submitted for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

Grant Forman

20th November, 1998.

Acknowledgments

I would like to thank my supervisor, Dr Martin Banwell, for his oversight of the research work reported here-in. I am very grateful for the guidance, enthusiasm and professionalism he provided during my course of study. The opportunity that he provided for me to study at the Australian National University is also much appreciated.

Thanks also to Dr Gregg Whited of Genencor International (South San Francisco) for providing generous samples of the various *cis*-1,2-dihydrocatechols used as starting materials in all of the research work described in this thesis.

I would also like to thank the members of the Synthesis and Mechanism Group, who have made my time in the Research School of Chemistry an enjoyable experience. Special thanks goes to Dr Jeff Holman, Dr Bernard Flynn and Dr Malcom McLeod for their time and knowledge. I would also like to thank Mr Chris De Savi for his support and friendship both inside and outside the work place. I am indebted to my two lab partners, Dr Chinh Bui and Mr Rajaratnam Premraj for their friendship, humour and professionalism.

For technical support, I would like to thank Mr Rob Longmore (GC) and Mr Tony Hearlt (HPLC). Their expertise and knowledge have helped my research to run a lot more smoothly than might otherwise have been the case. I am also grateful to Dr David Hockless for the speedy acquisition of X-ray crystallographic data. Thank you also to Mrs Joanne Harvey and Mr Brett Bissett for giving up their time to proof-read this manuscript.

Last, but certainly not least I would like to thank my family, Craig and Mike Forman for their support and encouragement. Special thanks to Akiko for her support and love.

"Nothing Great Was Ever Achieved Without Enthusiasm."

-Ralph Waldo Emerson.

Abstract

This thesis describes the exploitation of microbially-derived *cis*-1,2-dihydrocatechols as starting materials for the synthesis of chiral (non-racemic) cyclopropanes.

Chapter One provides an overview of the importance of chiral (non-racemic) cyclopropanes and the methods currently available for their synthesis. The potential of *cis*-1,2-dihydrocatechols to act as precursors of cyclopropanes is then discussed and accompanied by a commentary on the manner in which the former compounds are generated and currently exploited in chemical synthesis.

Chapter Two details a study of various different ways in which the nitrile-containing *cis*-1,2-dihydrocatechol derivative **63** can be cyclopropanated as well as the manner in which certain of the resulting cyclopropanes can be manipulated.

Chapter Three describes work which capitalizes on the results outlined in the previous one and which has led to the synthesis of the industrially important pyrethroid synthon **87** from the brominated *cis*-1,2-dihydrocatechol **14** (X=Br).

The work described in Chapter Four is concerned with elaborating the toluene-derived *cis*-1,2-dihydrocatechol **17** to analogues (e.g. **111**) of presqualene diphosphate (PSDP, **112**), a biologically significant monochiral cyclopropane.

Chapter Five outlines work directed towards construction of the polycyclopropyl arrays associated with the structurally unique and biologically significant natural products FR-900848 (**180**) and U-106305 (**181**). The starting materials used in these studies were the *cis*-1,2-dihydrocatechols **14** (X=I) and **16** derived by microbial oxidation of iodobenzene and *p*-iodotoluene respectively.

The final section of this thesis (Chapter Six) details the experimental procedures developed in connection with the work described in Chapters Two-Five.

Publications and Presentations Derived From Work Carried Out During the Period of PhD Candidature

Publications:

"(3a*R*,3b*S*,4a*R*,4b*R*,5a*R*,5b*S*)-4,4,5,5-Tetrabromo-2,2-dimethylperhydrodicyclopropa[*e*,*g*]-1,3-benzodioxole-3b-carbonitrile"

Banwell, M. G.; Forman, G. S.; Hockless, D. *Acta Cryst.* **1996**, *C52*, 1804.

"Chemoenzymatic routes to chiral (non-racemic) cyclopropanes. Preparation of a key intermediate for the synthesis of (1*R*)-*cis*-pyrethroids"

Banwell, M. G.; Forman, G. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2565.

Presentation:

"Chemoenzymatic Routes to Enantiopure Cyclopropanes."

Oral Presentation given at the Royal Australian Chemical Institute 16th National Organic Division Conference, July, 1998.

Glossary

The following abbreviations have been used throughout this thesis:

2D	two dimensional
Ac	acetyl
ACC	1-aminocyclopropane-1-carboxylic acid
AIDS	acquired immuno-deficiency syndrome
app.	apparent (^{1}H NMR spectra)
APT	attached proton test
Ar	aryl
AR	analytical reagent
aq.	aqueous
atm.	atmosphere
Bn	benzyl
Bu	butyl
Bz	benzoyl
c	concentration (g/100 mL)
ca.	circa (approximately)
cat.	catalyst
CETP	cholesteryl ester transfer protein
CI	chemical ionization
conc.	concentrated
m-CPBA	*m*-chloroperbenzoic acid
δ	chemical shift (parts per million)
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride

DMAP	4-*N*,*N*-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EFE	ethylene-forming enzyme
EI	electron impact
equiv.	equivalents
ether	diethyl ether
Et	ethyl
etc.	et cetera (and so on)
eV	electron volt
GC	gas chromatography
h	hour(s)
HETCOR	heteronuclear correlation spectroscopy
HIV	human immuno-deficiency virus
HMG-CoA	hydroxymethylglutaryl-CoA
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IC_{50}	concentration required for 50% inhibition of substrate
IR	infrared
J	coupling constant (Hz)
LD_{50}	lethal dose required to kill 50% of a population
LDA	lithium diisopropylamine
LDL-C	low density lipoprotein cholesterol
$M^{+\cdot}$	molecular ion (mass spectra)
Me	methyl
MEPY	methyl 2-pyrrolidone-5-carboxylate

m.p.	melting point (°C)
min	minutes
Ms	methanesulfonyl
MS	mass spectrum
m/z	mass-to-charge ratio
NADPH	nicotinamide adenine dinucleotide phosphate hydride
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ν_{max}	infrared absorbance maxima (cm^{-1})
ORTEP	Oak Ridge Thermal Elipsoid Plot
petrol	petroleum spirits (40-60 °C)
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMA	phorbol myristate acetate
PMB	*p*-methoxybenzyl
PKC	protein kinase C
PP_i	inorganic pyrophosphate
PPV	poly(1,4-phenylenevinylene)
*i*Pr	*iso*-propyl
pyr.	pyridine
PSDP	presqualene diphosphate
R*f*	retardation factor
R*t*	retention time
Red-Al®	sodium dihydro*bis*(2-methoxyethoxy)aluminate
RNA	ribonucleic acid
tRNA	transfer ribonucleic acid
ROMP	ring-opening metathesis polymerization
rt	room temperature

sh	shoulder (infrared spectra)
SFORD	single frequency off resonance decoupling
SQS	squalene synthase
TBAF	*tetra-n*-butylammonium fluoride
temp.	temperature
TPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEBAC	benzyltriethylammonium chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'-tetra*methylethylenediamine
TMS	trimethylsilyl
TPAP	*tetra-iso*-propylammonium perruthenate (VII)
p-Ts	*p*-toluenesulfonyl
p-TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
V	volts
vide infra	refer to below
viz.	*videlicit* (namely)
wt	weight
<	less than
>	greater than

TABLE OF CONTENTS

Chapter Three: Preparation of a Key Intermediate for the Synthesis of (1*R*, *cis*)-Pyrethroids

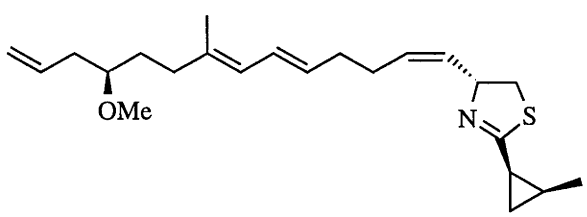
Chapter Four: Chemoenzymatic Synthesis of Presqualene Diphosphate Analogues

CHAPTER ONE

Introduction

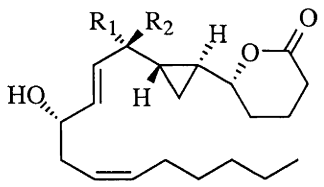
1.1 Biologically Significant Cyclopropyl Compounds

The highly strained but generally readily accessible cyclopropane ring-system has proven to be a useful building block for the stereo-controlled synthesis of a wide range of both cyclic and open-chain compounds.[1] This ring-system is also often incorporated into synthetically derived compounds of biological interest.[2] In addition, these three-membered carbocycles are frequently encountered as key structural components within a diverse range of naturally occurring compounds,[3] including those of marine origin.[4] For example, the novel cytotoxic agent curacin A (**1**), isolated by Gerwick *et. al.* in 1994, has generated significant interest within the scientific community[5] and it is the most prominent member of a small family[6] of potent antimitotic lipids isolated from the Caribbean marine cyano bacterium *Lyngbya majuscula*. The compound consists of a disubstituted thiazoline ring bearing a chiral cyclopropane ring and an aliphatic side-chain with a single stereogenic centre. Curacin A exerts its anti-proliferative effects through a high-affinity association with the colchicine-binding site of the cytoskeletal protein tubulin.[7] This result is intriguing because curacin A has little structural similarity to the alkaloid colchicine.



1

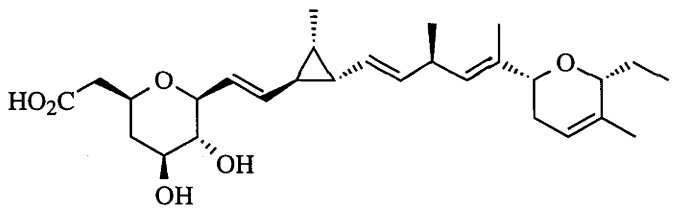
Constanolactones A and B (**2** and **3**, respectively), which were isolated from the marine red alga *Constantinea simplex* harvested off the west-coast of the United States, are cyclopropane-containing eicosanoids.[8,9] These compounds and other cyclopropanated oxylipins each contain twenty carbon atoms and are probably biosynthesized from arachidonic acid and eicosapetanenoic acid. As such they are thought to be representative products associated with a general pathway in marine prostanoid biosynthesis.[4,10-12]



2, constanolactone A: $R_1 = OH$, $R_2 = H$

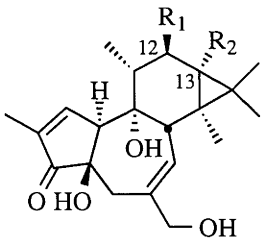
3, constanolactone B: $R_1 = H$, $R_2 = OH$

Ambruticin (**4**) is a representative member of a new class of antibiotics isolated from a bacterium belonging to the class *Myxobacteriales*.[13] This compound is highly active against systematic medical pathogens such as *Coccidioides imitus*, *Histoplasma capsulatum* and *Blastomyces dermatitidis* as well the dermatophytic filamentous fungi. As a consequence, ambruticin has attracted much attention from synthesis chemists and a significant challenge associated with the preparation of this compound involves the stereo-controlled assembly of the central cyclopropane ring.[14]



4

Derivatives of cyclopropanated diterpene phorbol (**5**) such as phorbol myristate acetate (PMA, **6**) are recognized as important compounds for controlling all intracellular signal transduction that is mediated through protein kinase C (PKC).[15] Recently, the related compound prostratin (**7**) has also attracted attention because of its anti-HIV activity.[16] Photolabile phorbol esters in which there is a diazoacetyl group at positions 12 or 13 have been synthesized from phorbol and found to bind with significant affinity to the peptide residue (the so-called peptide C domain) incorporating the phorbol ester-binding domain of PKC.[17] As a consequence such phorbol ester derivatives could be exploited for photoaffinity labelling of peptide C.



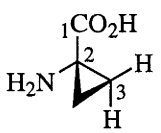
5, phorbol: $R_1 = R_2 =$ OH

6, PMA: $R_1 = OCO(CH_2)_{12}CH_3$, $R_2 = OCOCH_3$

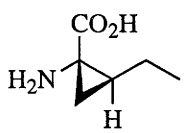
7, prostratin : $R_1 = H$, $R_2 = OCOCH_3$

There is also considerable interest in the biological properties of non-natural cyclopropyl-containing compounds. For example, replacement of proteogenic amino acids by their 2,3-methano- or cyclopropyl-amino acid equivalents within a peptide chain should lead to conformationally restricted analogues that might have rather different and possibly biologically significant properties.[18-20] Such "peptidomimetics" offer possibilities as biosynthetic and mechanistic probes[21,22] and, since the cyclopropane ring is probably capable of interacting with both nucleophiles and electrophiles, such cyclopropyl compounds could act as suicide inhibitors of various enzymatic processes.[23]

A number of naturally occurring 1-aminocyclopropane-1-carboxylic acids (ACC's) are known including the "parent" system **8**. The chiral ethyl derivative, **9**, which is known as coronamic acid, is obtained by hydrolysis of the plant toxin coronatine.[24] Both synthetic and naturally occurring 2,3-methanoamino acids are of great biological interest and include compounds which inhibit ethylene-forming enzyme (EFE),[25] amino transferase,[26] tryptophane hydrolase,[27] Dopa decarboxylase,[28] histadine decarboxylase,[29] and carboxypeptidase.[23] The majority of these fascinating compounds contain optically active cyclopropane units.



8 (ACC)

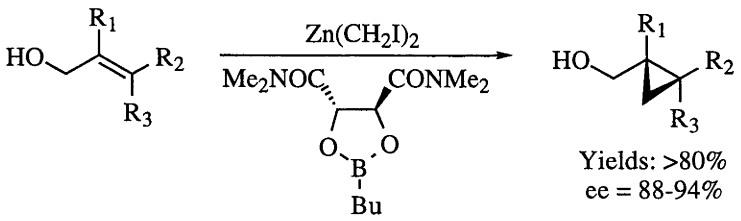


9 (coronamic acid)

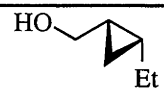
1.2 Methods for the Synthesis of Enantiopure Cyclopropanes

Dramatic advances in the understanding of biological processes at the molecular level have generated a significant demand for enantioselective syntheses of natural products and related therapeutic agents. This situation presents exciting challenges in organic synthesis.[30] As part of this demand there is a real need for enantioselective routes to monochiral cyclopropanes and the following paragraphs outline established work in this area.

Besides resolution of their racemates, various synthetic methods have been used for preparing optically active cyclopropanes, some of which are now conducted on an industrial scale.[31] Stoichiometric chiral reagents have been developed for the enantioselective cyclopropanation of allylic alcohols[32,33] with the most efficient system discovered to date involving the dioxaboralane **10** (**Scheme 1.1**), a bifunctional, chiral (non-racemic) ligand containing both an acidic and basic site that allow for simultaneous chelation of the acidic Simmons-Smith reagent[34] and the basic allylic alcohol. As a consequence, highly enantioselective Simmons-Smith cyclopropanation reactions can be conducted on a wide range of allylic alcohols.

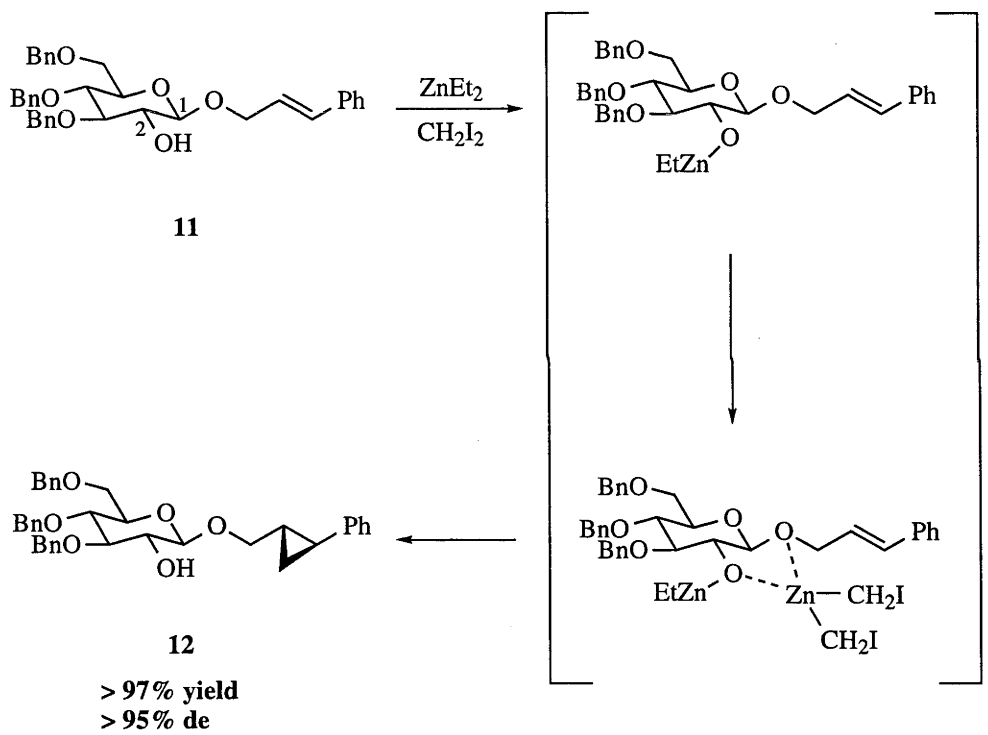


10

Product	Yield	Enantioselectivity
	>98%	ee = 93%
	90%	ee = 93%
	85%	ee = 94%

Scheme 1.1: *Asymmetric Simmons-Smith Cyclopropanations of Various Allylic Alcohols using Dioxaboralane* **10**.

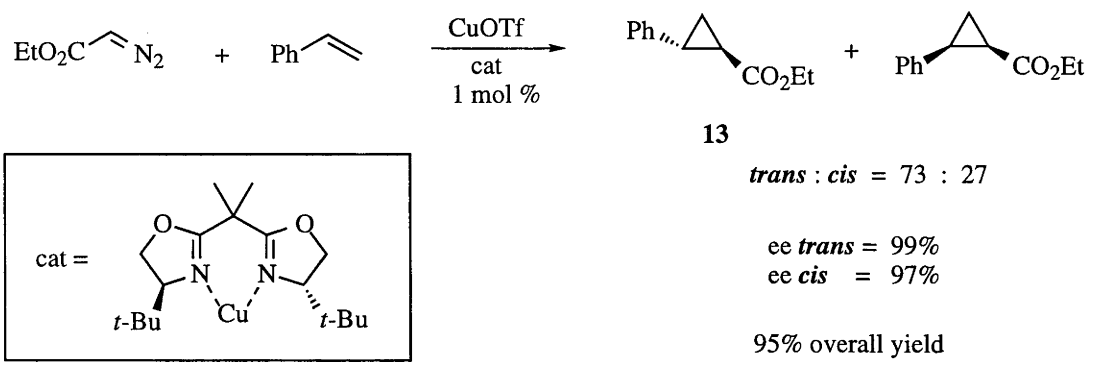
Recently, carbohydrate-derived auxiliaries have been employed for the Simmons-Smith cyclopropanation reaction.[32,35] For example, extremely high diastereoselectivities were observed in the cyclopropanation of the glycosylated cinnamyl alcohol **11** using an excess of diethylzinc and diiodomethane (**Scheme 1.2**). Studies have shown that the key structural elements of the β-D-glucose auxiliary that dictate the absolute stereochemistry associated with the product cyclopropane **12** are the C-1 oxygen and the unprotected alcohol at C-2, with the latter forming the corresponding ethylzinc alkoxide with one equivalent of $ZnEt_2$. This alkoxide is an efficient bidentate ligand for complexing a second equivalent of the active cyclopropanating agent, which is probably *bis*(iodomethyl)zinc.[35g]



Scheme 1.2

The synthesis of enantiomerically-enriched cyclopropanes can also be achieved by using transition-metal based carbenoid reagents to effect cyclopropanation of prochiral alkenes. Particularly successful methods have been developed by Davies,[36] Evans,[37] Masamune,[38] Pfaltz,[39] and Doyle.[40] For example (**Scheme 1.3**), in the presence of the carbenoid precursor ethyl diazoacetate, styrene is converted into the corresponding

trans-carboxyl-substituted cyclopropane **13** in 99% ee using only 1 mol% of the appropriate copper catalyst. Despite these impressive results, the transition-metal catalyzed addition of carbenoids to alkenes suffer from a serious drawback, namely, the requirement that diazo-carbonyl compounds be used as the cyclopropanating agents meaning that products are restricted to carbonyl-containing cyclopropanes. To date, and not through lack of effort,[41] no efficient means for the enantioselective delivery of simple methylene has been achieved using precursor diazo compounds.



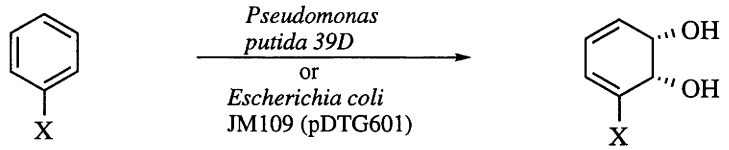
Scheme 1.3

1.3 Biocatalytic Production of *cis*-1,2-Dihydrocatechols

cis-1,2-Dihydrocatechols of the general type **14** offer interesting possibilities as starting materials for the synthesis of enantiopure cyclopropyl compounds. However, before such possibilities are enunciated it is necessary to provide a commentary on the production and general utility of these compounds.

In 1968, Gibson's group[42-45] elucidated the oxidative pathway by which many aromatic compounds are degraded by the soil micro-organism *Pseudomonas putida* (**Scheme 1.4**).[46] The ferrodoxin-based enzyme systems responsible for these fascinating conversions have been named dioxygenases and are generally found in procaryotes. As part of Gibson's research, he identified a chemically mutated form (39D) of *Pseudomonas putida* that lacked the dehydrogenase enzyme responsible for carrying the primary product of arene oxidation, *viz.* the *cis*-1,2-dihydrocatechol **14**, further downstream. As a consequence when arenes are presented to this mutant

organism significant quantities of diols of the general type **14** can be accumulated. Further, Gibson established that the product of oxidation of toluene, *viz.* compound **14** (X=Me), is an enantiomerically pure compound which possesses the illustrated absolute configuration.[46] Since the original work in this area it has been shown that many arenes are *cis*-dihydroxylated, in a completely regio- and enantio-selective manner, by the toluene-dioxygenase enzyme system.[47]



X = Cl, Br, I, CN, Me *etc.* **14**

Scheme 1.4: *Biotransformation of Arenes by Micro-organisms Containing the Toluene-Dioxygenase Enzyme System.*

Although *Pseudomonas putida* 39D is the most commonly exploited micro-organism for this type of conversion others are available. In fact the process has now been refined to such an extent that recombinant gene technology[48] allows for the production of *E. coli* cells which over-express the dioxygenase enzyme responsible for this oxidation process, thereby allowing for highly efficient production (up to 35 g of product/litre of fermentation broth) of various *cis*-1,2-dihydrocatechols. To date, more than two hundred and fifty metabolites produced by dioxygenase-mediated oxidation of aromatics have been reported.[49] Some examples of metabolites generated from mono- and poly-nuclear aromatic substrates are shown in **Figure 1.1**.

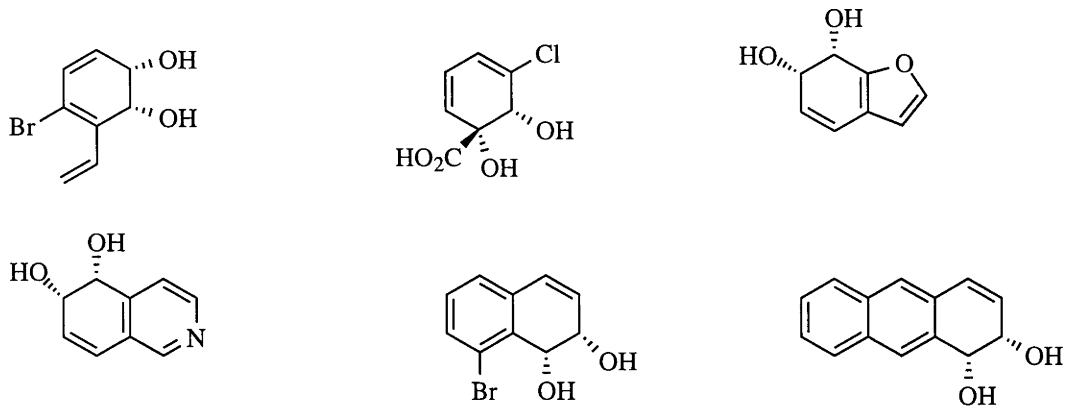
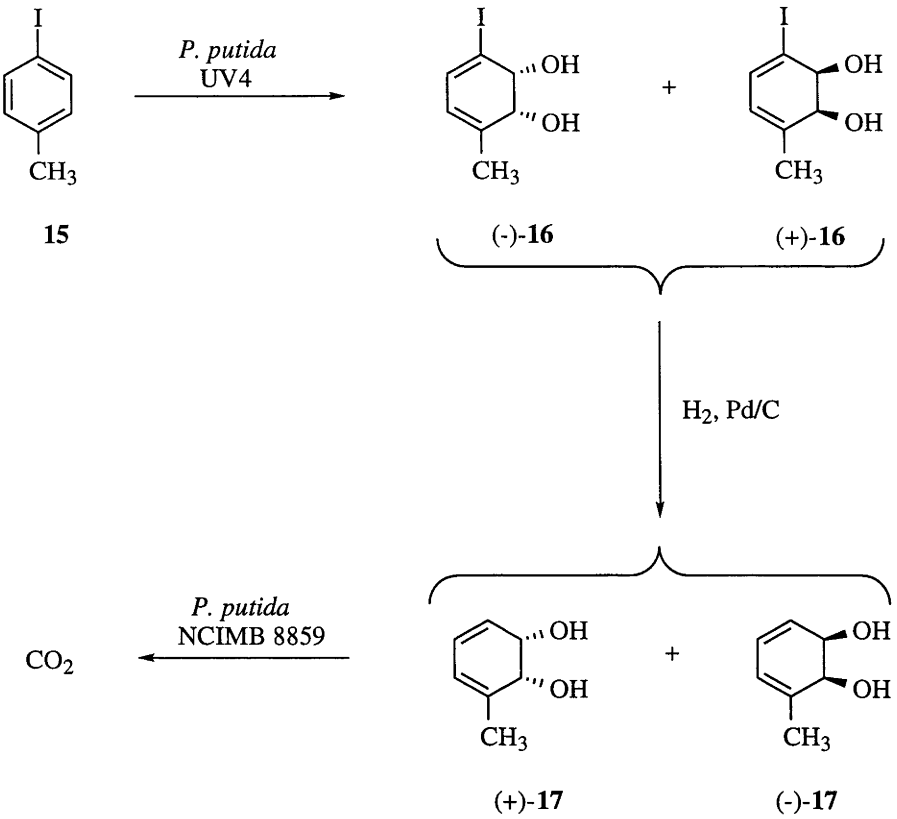


Figure 1.1: *Examples of Arene Metabolites Formed* via *P. putida 39/D and/or E. coli* JM 109 (pDTG601) *Toluene Dioxygenase-Catalyzed Degradation of Polynuclear Aromatic Compounds.*

The outcome of any particular biotransformation is dependant upon both the electronic nature and size of the substituents attached to the aromatic ring undergoing reaction.[50] For example, microbial oxidation of toluene affords *cis*-1,2-dihydrocatechol (+)-**17**, while reaction of *p*-iodotoluene **15** (with *Pseudomonas putida* UV4) provides a *ca.* 90:10 mixture of the diols (+)-**16** and (-)-**16**. Thus, in the latter transformation, the more bulky iodine atom present within substrate **15** provides the main stereodirecting effect (**Scheme 1.5**).[51] Interestingly, monochiral diol (-)-**17**, *viz.* the enantiomer of the compound obtained by direct microbial oxidation of toluene, is generated by hydrogenolytic cleavage of the C-I bond in diols (+)-**16** and (-)-**16**. The resulting 90:10 mixture of toluene diols (+)-**17** and (-)-**17** is then treated with *Pseudomonas putida* NCIMB 8859 which selectively dehydrogenates the minor enantiomer and further degrades the resulting catechol to carbon dioxide. As a consequence, pure diol (-)-**17** is left behind.[52]



Scheme 1.5

The biotransformations described above are considered to be "environmentally friendly" or "green" since the conversion consumes potentially hazardous aromatic compounds. Furthermore, these transformations underscore the potential of biocatalysis and the use of enzymes to achieve selective organic transformations and, thereby, reducing the waste stream.[49] The enzymatic preparation of chiral compounds can, in a single reaction step, produce a relatively complex species with defined absolute stereochemistry and all this in an aqueous medium.

1.4 Synthetic Applications of *cis*-1,2-Dihydrocatechols

The *cis*-1,2-dihydrocatechols derived from aromatic compounds show considerable promise as starting materials for the development of both efficient and enantiospecific routes to a structurally diverse range of compounds. Given the multiple functionalities contained within *cis*-1,2-dihydrocatechols of the type **14**, there are a number of

stereocontrolled transformations possible. The vicinal-*cis*-diol moiety offers the potential to control the facial selectivity of reactions involving additions to the carbon-carbon double-bonds within compounds **14** and thereby dictating the stereochemistries of the newly formed stereogenic centres. Thus, through chelation control the unprotected *cis*-diol unit can direct attack to the *syn*-face of the diene unit, while the steric demands of diol protecting groups such as acetonides normally directs attack to the *anti*-face of the diene unit. Furthermore, the substituent X on the diene unit generally strongly differentiates the two double bonds such that one of these is generally attacked preferentially in electrophilic addition reactions. This same substituent also strongly influences the regioselectivity of Diels-Alder and other cycloaddition reactions. The steric demands of the substituent X can also permit selective mono-protection/derivatization of the hydroxyl group remote from it. In an overall sense, then, these various structural elements generally allow for highly controlled reactions of the *cis*-1,2-dihydrocatechols.

To date, the only commercially manufactured products which are known to exploit an arene *cis*-diol derivative as a synthetic intermediate are those illustrated in **Figures 1.2** and **1.3**. In 1995 Genencor reported the "green" manufacture of indigo **19** *via* the indole-derived *cis*-2,3-dihydrodiol **18** which was obtained using a recombinant strain of *E. coli* containing naphthalene dioxygenase cloned from a *Pseudomonas putida*

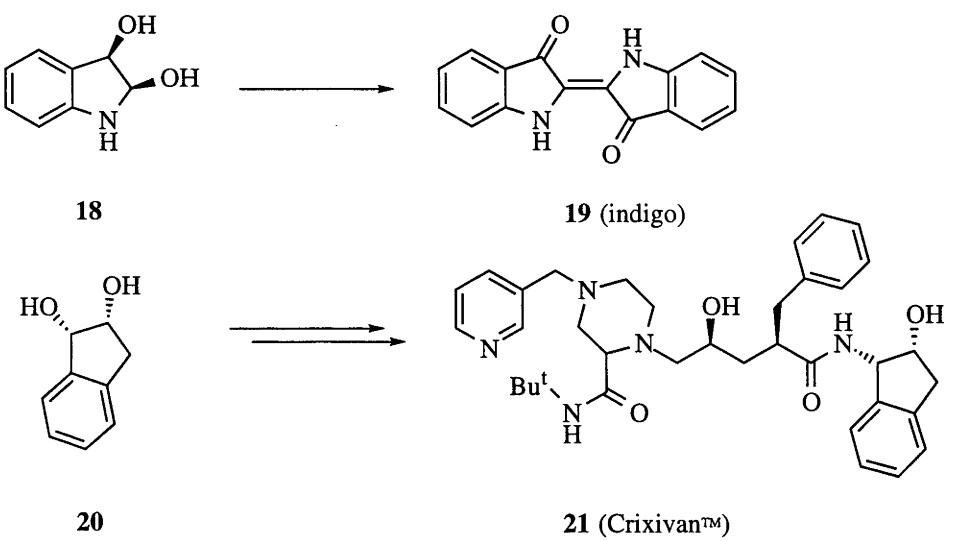


Figure 1.2: *Commercial Applications of* cis-*1,2-Dihydrocatechols.*

species.[53] More recently, Merck have produced the HIV protease inhibitor indinavir (Crixivan™, **21**) using, as a key intermediate, the diol **20** obtained by microbial oxidation of indene.[54]

Within the realm of polymer chemistry, formation of high purity polyphenylene **23** from benzene *cis*-1,2-dihydrocatechol **22** was first reported in 1983 (**Figure 1.3**).[55] More recently, a related synthesis of poly(1,4-phenylenevinylene) (PPV[56], **26**), based on the *living* ring-opening metathesis polymerization (ROMP)[57] of bicyclo[2.2.2]octadiene derivative **24**, has been developed by Grubbs *et al.*[58] Thus, Diels-Alder elaboration of 3,5-cyclohexadiene-*cis*-1,2-diol **22** afforded *bis*(carboxylate) derivative **24**, which was subjected to ring-opening polymerization to provide polymer **25**. This latter material was converted into the commercially significant copolymer PPV (**26**) by thermolytic extrusion of carbon dioxide and methanol.

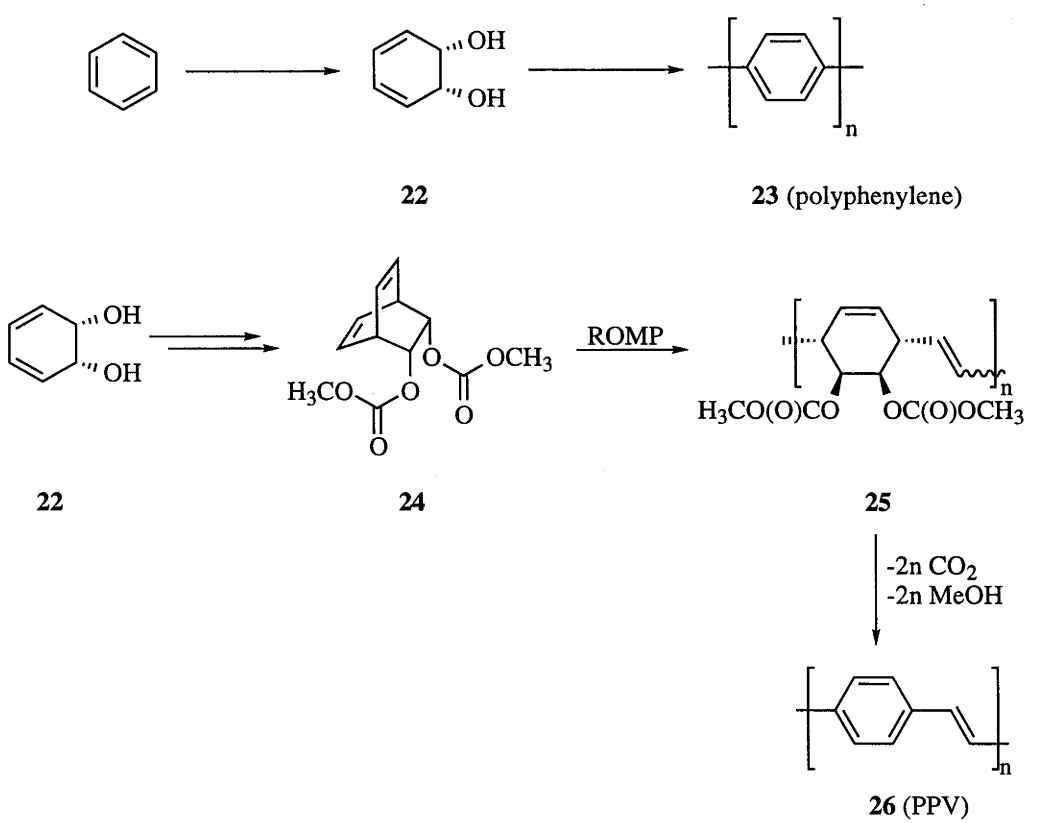
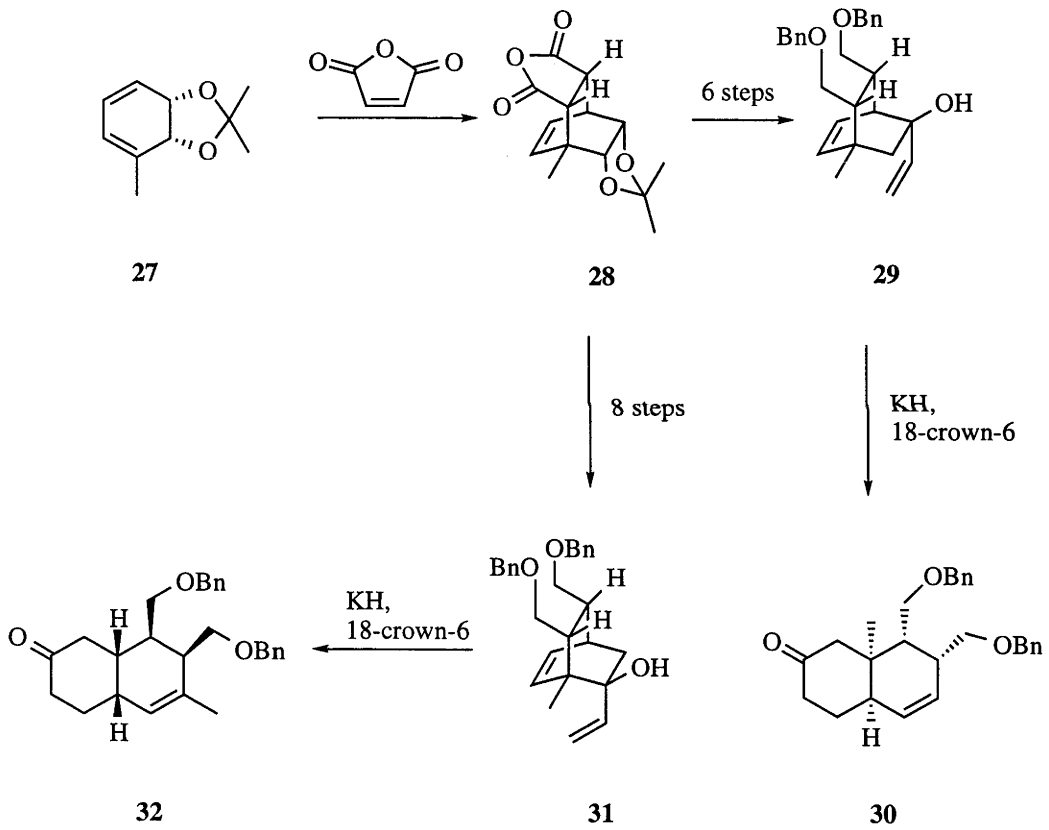


Figure 1.3: *The Application of* cis-*1,2-Dihydrocatechol* **22** *to Polymer Chemistry.*

The ready capacity of *cis*-1,2-dihydrocatechols such as **14** to engage, as the 4π component, in diastereofacially selective Diels-Alder cycloaddition reactions with the consequent formation of bicyclo[2.2.2]octenes[59] has prompted efforts to investigate the elaboration of these adducts to decalin, steroid and taxoid skeleta.[60-63] For example, the simple *cis*-1,2-dihydrocatechol derivative **27** was converted, *via* reaction sequences involving Diels-Alder cycloaddition and anionic oxy-Cope rearrangement steps, into the enantiopure decalin **30** (**Scheme 1.6**).[60] By using simple modifications of this chemistry the *pseudo*-enantiomer, **32**, of decalin **30** was also able to be prepared from acetonide **27**.

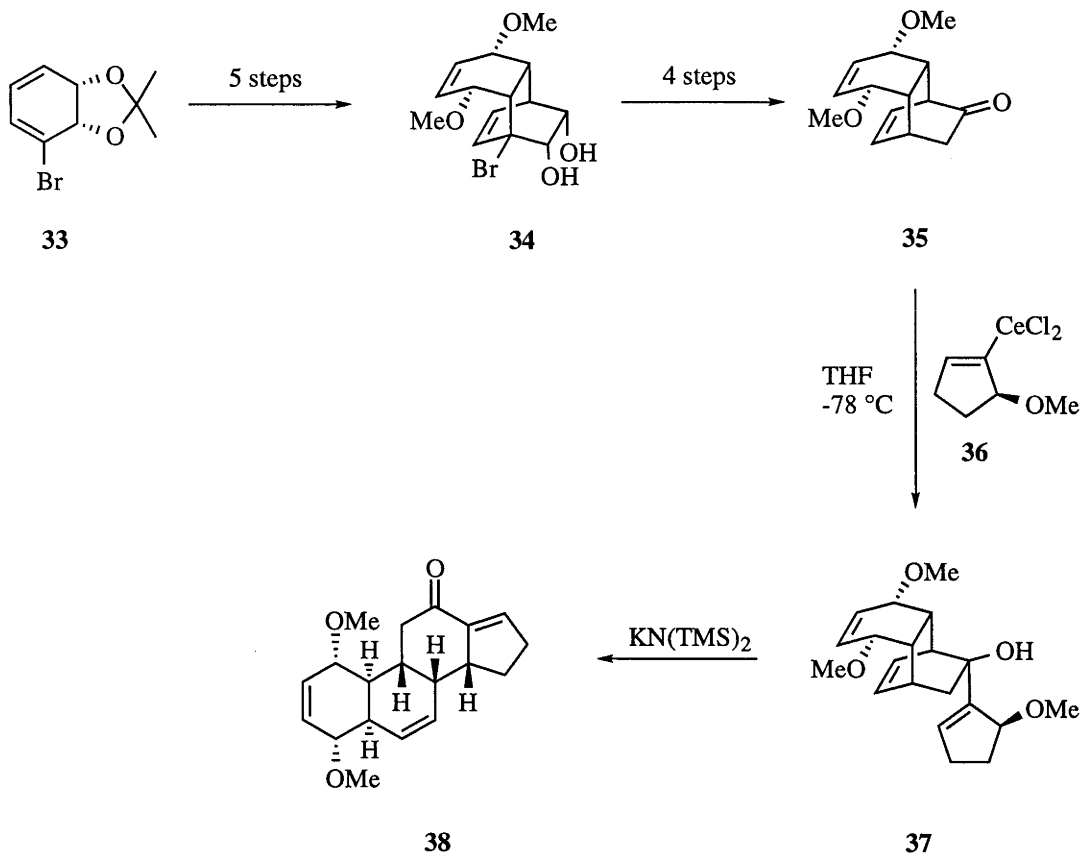


27 28 29 32 31 30

Scheme 1.6

A Diels-Alder cycloaddition reaction between bromoacetal **33** (**Scheme 1.7**) and *p*-benzoquinone afforded a single adduct which, after five simple chemical steps, was converted into compound **34**. The diol moiety within this bicyclo[2.2.2]octanyl-containing system was then manipulated so as to give ketone **35**. Addition of the chiral

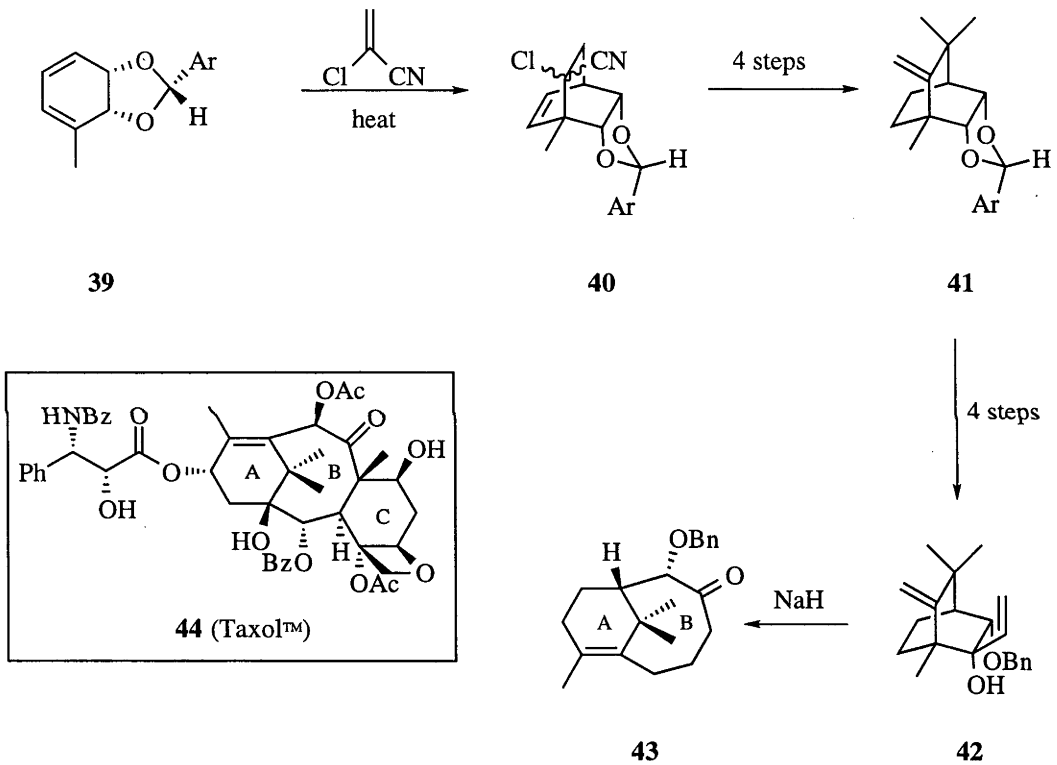
organocerium reagent **36** to this last compound proceeded with high diastereofacial selectivity to provide the 1,5-dien-3-ol **37** which upon anionic oxy-Cope rearrangement and subsequent loss of methoxide ion afforded the highly functionalized steroidal nucleus **38**. The enantiomer of compound **38** could also be prepared by the addition of the optical antipode of the organocerium reagent **36** to *ent*-**35** (itself available through straightforward manipulation of diol **34**) thus providing an enantiodivergent approach to novel steroidal systems.[61]



Scheme 1.7

A concise synthesis of the AB-ring substructure associated with the enantiomer of paclitaxel (Taxol™, **44**), which was inspired by the challenge of securing a short route to this powerful antimitotic agent,[62] is outlined in **Scheme 1.8**. Thus, a Diels-Alder cycloaddition reaction between *p*-methoxybenzylidene acetal **39** (which is readily obtained from *cis*-1,2-dihydrocatechol **17**) and α-chloroacrylonitrile afforded a 4:1 epimeric mixture of *ortho*-adducts **40** which were manipulated, over four steps, to give

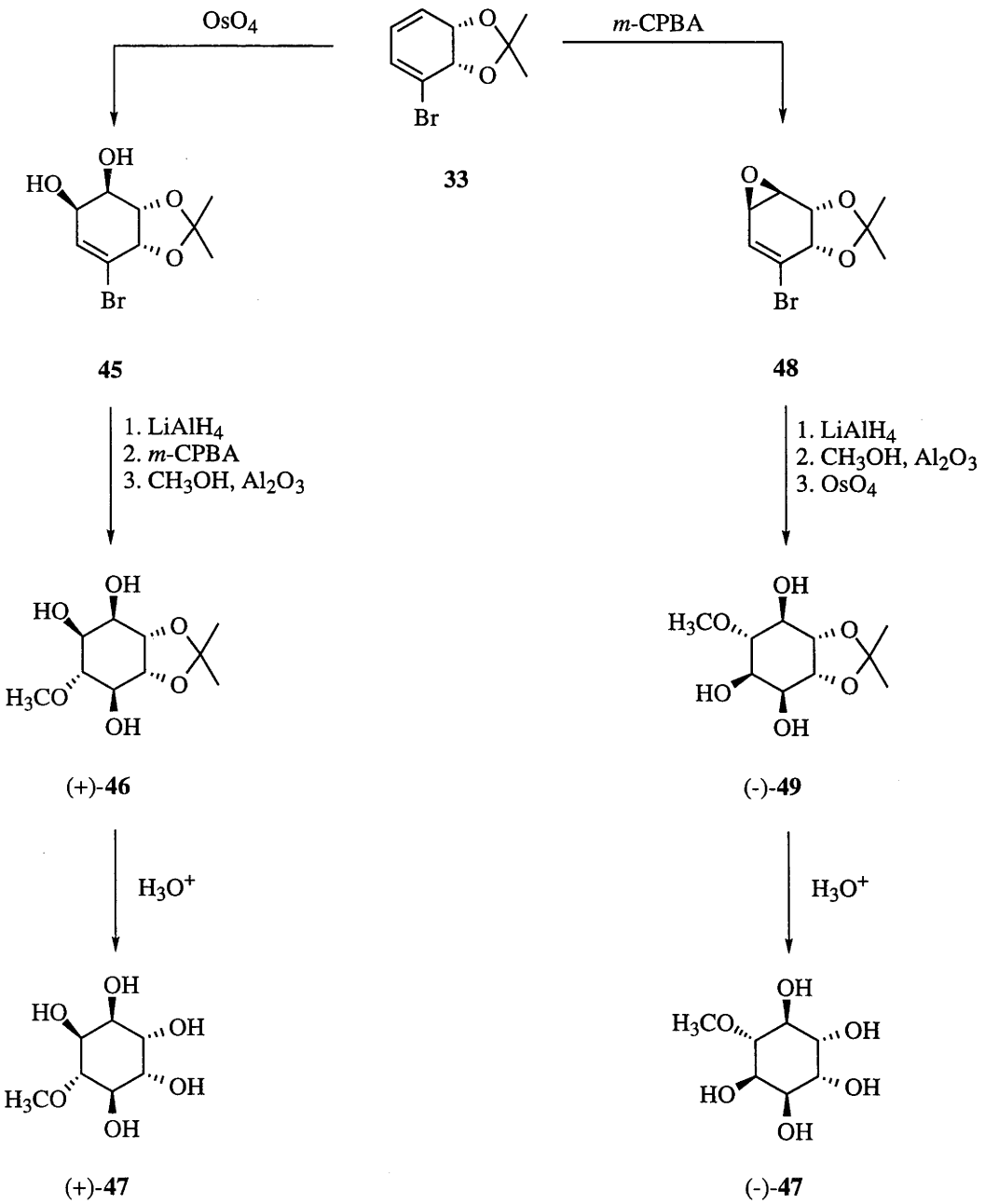
the methylenated compound **41**. Further chemical transformations of this latter compound then afforded the 1,5-dien-3-ol **42** which underwent anionic oxy-Cope rearrangement upon treatment with sodium hydride to provide the *gem*-dimethylated bicyclo[5.3.1]undecene system **43**.[63] The protocol just described provides, in a concise fashion, access to the AB-ring framework associated with *ent*-paclitaxel. Since the compound ***ent*-39** is also available (in *ca.* 98% ee), *via* a two-step sequence involving microbial oxidation of *p*-iodotoluene and reductive iodination of the resulting *cis*-1,2-dihydrocatechol (see pages 9-10), then the enantiomer of compound **43** is also accessible by this same chemical pathway.



Scheme 1.8

Perhaps the most dramatic illustration of the hidden symmetry elements associated with the *cis*-1,2-dihydrocatechols is Hudlicky's enantiodivergent synthesis of the optical antipodes of pinitol, a cyclitol isolated from several plant sources (**Scheme 1.9**).[64,65] The pathways leading to these enantiomers are exactly the same in that they both start with compound **33** and use identical sets of reagents and conditions.

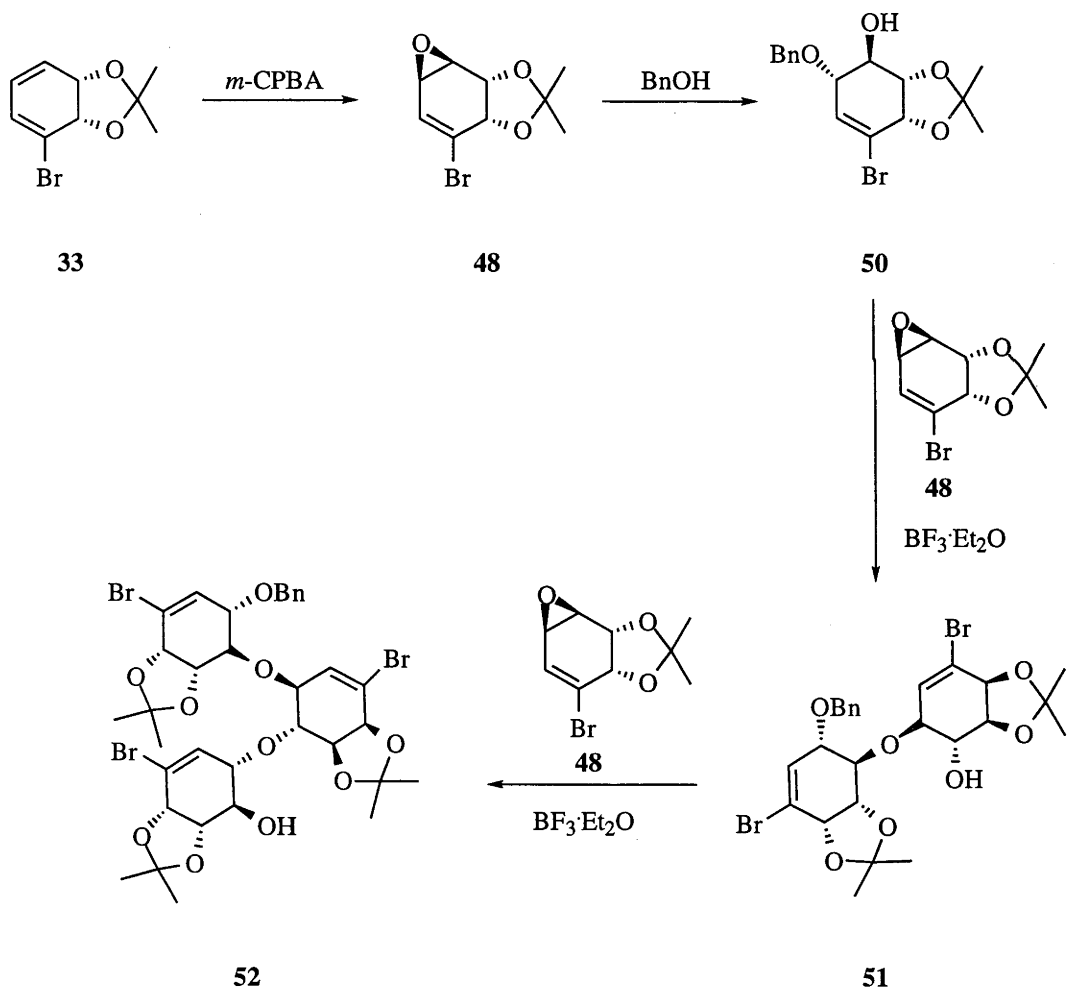
However, by simply changing the order in which the requisite steps of the reaction sequence were carried out, access to either enantiomer was possible. Thus, on the pathway to (+)-pinitol, the acetonide derivative, **33**, of *cis*-1,2-dihydrocatechol **14** (X=Br) was dihydroxylated and the resultant diol **45** reductively debrominated with lithium aluminium hydride. The ensuing disubstituted olefin was then subjected to hydroxy-directed epoxidation and subsequent alumina-promoted methanolysis of the



Scheme 1.9: *Enantiodivergent Syntheses of (+)- and (-)-Pinitol,* [*(+)- and (-)-***47**, *respectively*].

epoxide ring gave triol (+)-**46**. Hydrolytic cleavage of the acetonide moiety then provided (+)-pinitol [(+)-**47**]. By simply reordering the steps in the sequence enantiomer (-)-**47** could be obtained.

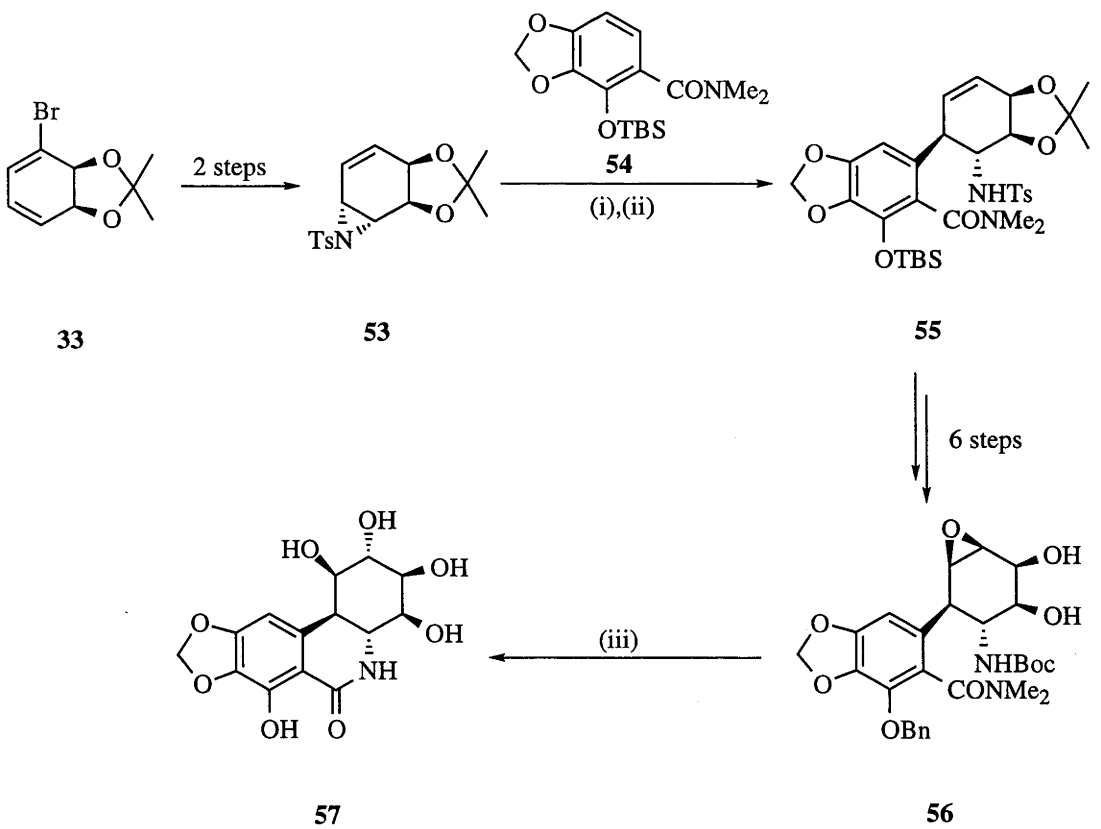
Recently, iterative methods for the synthesis of oligocyclitols, hydrolytically stable analogues of oligosaccharides which continue to gain attention because of their therapeutic potential, have been developed.[66-68] For example, alkenyl epoxide **48** (**Scheme 1.10**) and alcohol **50**, both of which are readily prepared from *cis*-1,2-dihydrocatechol derivative **33**, have been condensed with one another to give the conjugate **51**. This last compound could then be reacted with epoxide **48** to provide the novel carbocyclic nor-trisaccharide **52** (**Scheme 1.10**).



33 **48** **50** **48** **51** **52**

Scheme 1.10

In the alkaloid domain, the pharmaceutically important natural products lycoridine and pancratistatin (**57**) have recently been synthesized by an extraordinarily concise route that further demonstrates the utility of *cis*-1,2-dihydrocatechols in chemical synthesis.[69-72] The preparation of compound **57** (**Scheme 1.11**) began with subjection of the diene/acetonide **33** to the Jacobson-Evans aziridination[71] protocol. The tosyl aziridine **53** so-formed underwent coupling with the cuprate obtained by *ortho*-metallation of amide **54**. Further chemical manipulations of the resulting conjugate, **55**, then furnished the diol **56**, which, upon reaction with aqueous sodium benzoate, provided the naturally occurring and biologically active (+)-pancratistatin (**57**).



Scheme 1.11: *Reagents and Conditions*: (i) *s*-BuLi, TMEDA, THF, -78 °C. (ii) CuCN, -78 °C. (iii) sodium benzoate, H_2O.

1.5 Possibilities for the Synthesis of Enantiopure Cyclopropanes from *cis*-1,2-Dihydrocatechols

cis-1,2-Dihydrocatechols of the general type **14** offer interesting possibilities as starting materials for the synthesis of enantiopure cyclopropyl compounds. In principle, monocyclopropanation of diene **14** could lead to any one of four possible bicyclo[4.1.0]heptenes, *viz.* compounds **58-61** (**Figure 1.4**). If the X group associated with such compounds could be removed then the product derived from compound **60** would be the enantiomer of that derived from isomer **58**. Similarly, removal of the X group from within compound **61** would give the enantiomer of that compound obtained when the X-group was removed from isomer **59**. Alternatively (**Figure 1.5**), oxidative cleavage of the diol **58** would give open-chain dialdehyde

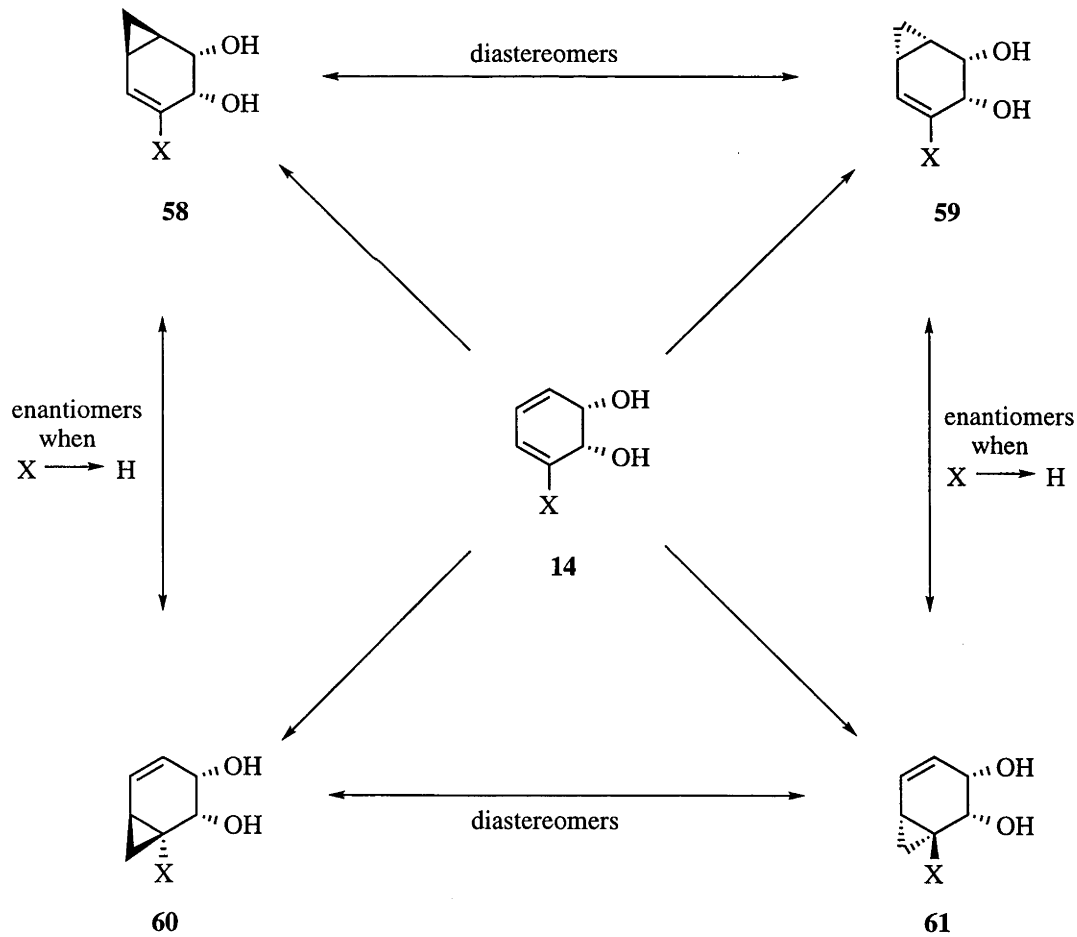


Figure 1.4: *Relationships between Four Possible Products Arising from Mono-Cyclopropanation of* cis-1,2-*Dihydrocatechol* **14**.

62 while similar treatment of compound **60** would give the enantiomeric dialdehyde *ent*-**62**. Related manipulation of isomers **59** and **61** would give the enantiomeric pair *ent*-**62**/**62**.

Remarkably, for all the substantial activity that has centred on exploiting microbially-derived *cis*-1,2-dihydrocatechols in chemical synthesis there has been almost no effort directed towards their use in the synthesis of chiral (non-racemic) cyclopropanes.[73-75]

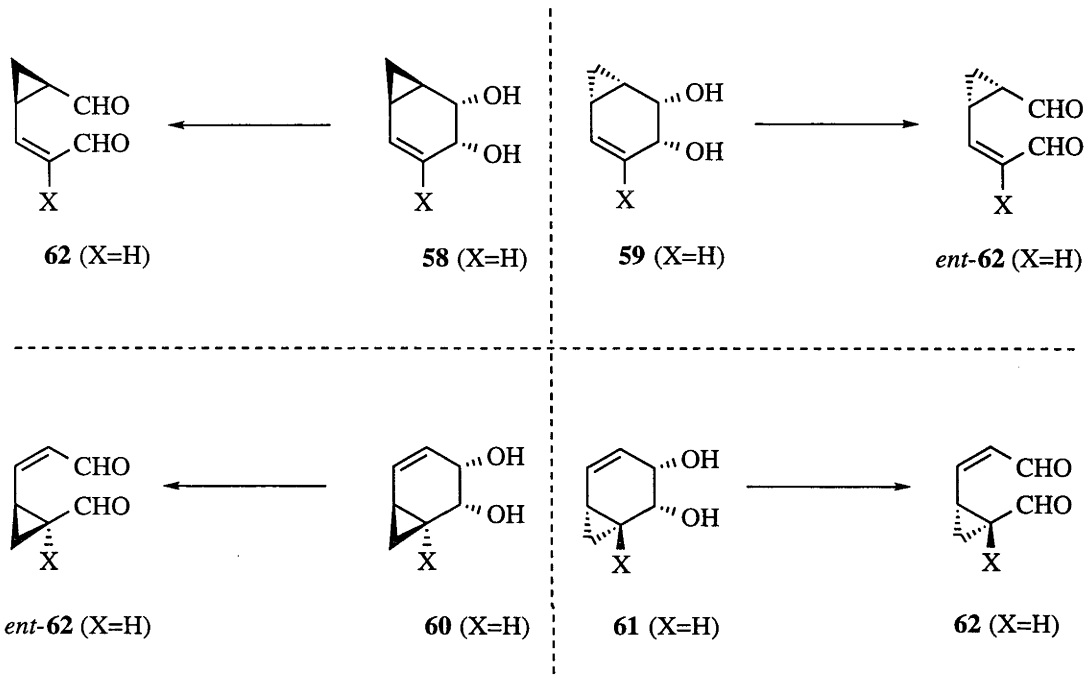


Figure 1.5: *Relationships Between Products Arising from Oxidative-Cleavage of Mono-Cyclopropanated* cis-1,2-*Dihydrocatechol Derivatives* **58-61**.

1.6 Aims of the Research Work Described in this Thesis

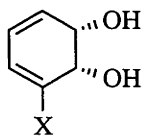
On the basis of the foregoing it would seem that the monochiral *cis*-1,2-dihydrocatechols **14** offer unique possibilities as far as the preparation of enantiopure cyclopropyl compounds are concerned. Consequently, the primary aim of the current study was to explore such possibilities, *viz.*, the synthesis of enantiopure cyclopropyl compounds from *cis*-1,2-dihydrocatechols. The following chapters describe the outcomes of such efforts.

CHAPTER TWO

An Investigation of Some Methods for Effecting Cyclopropanation of *cis*-1,2-Dihydrocatechols

2.1 Introduction

The pursuit of the aims enunciated in the previous chapter required an initial investigation of methods for effecting cyclopropanation of *cis*-1,2-dihydrocatechols of the general type **14**. Consequently, this chapter describes the outcomes of an examination of such reactions which have provided hitherto unreported mono-chiral cyclopropanes. Chemical modifications of certain of these compounds, in an attempt to provide enantiomeric pairs of non-ring-fused cyclopropanes, have also been examined.



14

X = Cl, Br, I, CN, Me *etc.*

2.2 Mono-cyclopropanation of *cis*-1,2-Dihydrocatechols: an Overview

In principle, there are three obvious and distinct ways in which mono-cyclopropanation of *cis*-1,2-dihydrocatechols of the general type **14** could be effected. Firstly, phase-transfer generated dihalogenocarbenes could react with these dienes and it might be anticipated that there would be some preference for these electrophilic species to add to the more-nucleophilic double-bond within diene **14**. In practice,[%] it has been shown that dichloro- and dibromo-carbenes do not react very effectively with the unprotected diols **14** - such reactions give a complicated mixture of adducts and it may be that under these circumstances carbene insertion into the OH bonds is complicating matters. In contrast, the readily prepared acetonide derivatives of **14** engage in a smooth reaction with such carbenes and cyclopropanation almost invariably takes place, as expected, at the less-substituted double-bond. The diastereo-facial selectivity associated with such reactions is also very high with addition taking place at that face of the double-bond opposite to the sterically demanding acetonide unit .[75]

[%] Unpublished observations within these laboratories, 1994-1995.

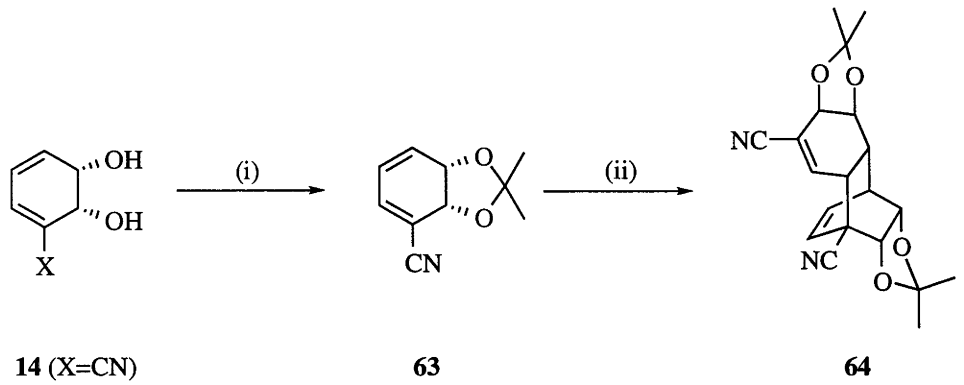
A regio-complementary outcome to the one just described might be expected if a good Michael acceptor was present in the molecule, as could be the case for the diene **14** (X=CN). Thus, nucleophilic cyclopropanation of such a compound, or perhaps the acetonide derivative there-of, might allow for introduction of a methylene bridge across the more substituted double-bond. Again, steric factors should ensure good diastereo-facial selectivity with the newly introduced cyclopropyl carbon and its associated substituents being delivered to that face of the double-bond opposite to the acetonide residue.

In principle, Simmons-Smith cyclopropanation of compounds of the general type **14** should allow cyclopropanation of the α-face of the double-bonds within these molecules through an hydroxy-directed processes. In practice, however, the Lewis-acidic conditions associated with this type of cyclopropanation reaction result in dehydration of the substrate and the formation of phenolic products which are of no relevance to the present objectives. Nevertheless, the nucleophilic and electrophilic cyclopropanation reactions described in the preceeding paragraphs appeared worthy of investigation and studies of such chemistry form the basis of the discussion in the following sections.

2.3 Nucleophilic Cyclopropanation of the Benzonitrile-derived *cis*-1,2-Dihydrocatechol

In an effort to examine the potential regio-chemical complementarity between the nucleophilic and electrophilic cyclopropanation reactions mentioned above the previously described[76] acetonide derivative, **63** (**Scheme 2.1**), of benzonitrile diol **14** (X=CN) was chosen as a substrate because it is unique amongst the readily available *cis*-1,2-dihydrocatechols in having a built-in Michael-acceptor. Interestingly, when benzonitrile diol derivative **63** was subjected to flash column chromatography dimerization occurred to give the Diels-Alder product **64** [54% from **14** (X=CN)]. The spectral data obtained for this compound were in full accord with those reported by Tran *et al.*,[76] and it is pertinent to note that analogous dimers have been obtained from

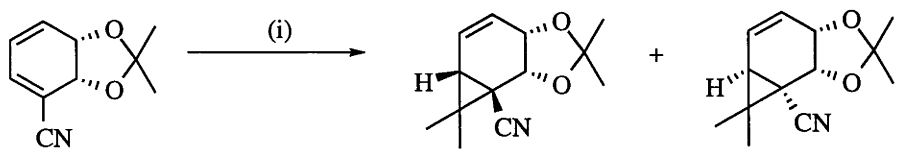
related *cis*-1,2-dihydrocatechol derivatives.[77] Nevertheless, dimerization could be avoided if compound **63** was used immediately after preparation.



14 (X=CN) **63** **64**

Scheme 2.1: *Reagents and Conditions*: (i) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (0.05 mole equiv.), 0 °C, 1 h. (ii) flash column chromatography, silica gel, 54% from **14** (X=CN).

The nucleophilic cyclopropanation of compound **63** was studied first. When this compound was reacted with diphenylsulfonium isopropylidene[78] ($Me_2C{=}SPh_2$), formed *in situ* by reaction of diphenylethylsulfonium tetrafluoroborate, methyl iodide and lithium diisopropylamine, then an inseparable mixture of two monocyclopropanation products, **65** (48%) and **66** (24%), was isolated after column chromatography (**Scheme 2.2**).# The structures of these compounds were established through spectroscopic and chemical correlation studies (see below). There are a number



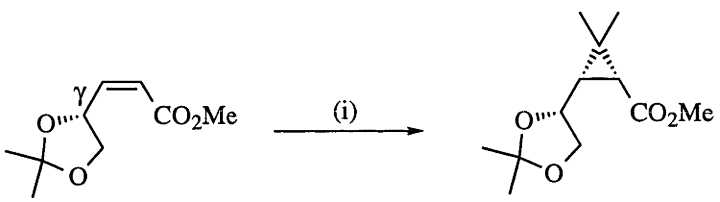
63 **65** **66**

Scheme 2.2: *Reagents and Conditions*: (i) diphenylethylsulfonium tetrafluoroborate (1.0 mole equiv.), LDA (1.1 mole equiv.), THF, DME, CH_2Cl_2 (5:5:1), -78 °C, 0.75 h then MeI (1.0 mole equiv.), 2 h then LDA (1.1 mole equiv.), -78 °C, 1.25 h, 72%.

of features of the reaction portrayed in **Scheme 2.2** that deserve comment. In keeping with expectation, cyclopropanation of the more-substituted double-bond within

Reaction first performed by Pallich, S. in these laboratories.

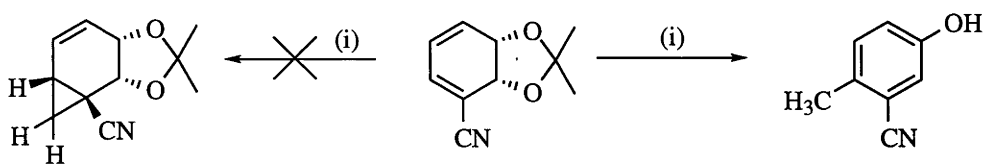
compound **63** had taken place but, rather surprisingly, there was a significant preference for reaction at the seemingly more congested α-face of this substrate. On the basis of these results, it would seem possible that there is a high-affinity association between the positively charged terminus of the isopropylidene substituted ylide and the oxygens contained within substrate **63**. A survey of the literature reveals that a similar diastereofacial selectivity by Krief *et al.* in the reaction of γ-alkoxy-α,β-unsaturated ester **67** with diphenylsulfonium isopropylidene which produced cyclopropane **68** (**Scheme 2.3**) as the exclusive product of reaction.[79] Thus, this reaction proceeds by a pathway in which the acetonide oxygen(s) of substrate **67** co-ordinate(s) to the ylide such that the sterically more-hindered cyclopropanation product, **68**, is obtained.



67 **68**

Scheme 2.3: *Reagents and Conditions*: (i) diphenylsulfonium isopropylidene (3.0 mole equiv.), DME, -78 °C, 0.4 h then -60 °C to -50 °C, 0.6 h then -50 °C to 20 °C.

The foregoing observations suggested that installation of a methylene-cyclopropyl moiety into nitrile **63**, so as to provide compound **69**, should be possible *via* reaction with dimethylsulfoxonium methylide.[80] To these ends, the acetonide **63** was treated with one equivalent of dimethylsulfoxonium methylide at room temperature (**Scheme 2.4**). However, after work-up, phenol **70** (76%) was the only isolable product of



69 **63** **70**

Scheme 2.4: *Reagents and Conditions*: (i) dimethylsulfoxonium iodide (1.5 mole equiv.), NaH, DMSO, -78 °C to 0 °C, 2 h, 76%.

reaction. It seems that under the reaction conditions, compound **63** engages in an addition/elimination reaction sequence (**Figure 2.1**) involving loss of one molar equivalent of acetone to provide intermediate **71** which, after aromatization *via* elimination of dimethylsulfoxide and protonation, gives rise to the observed product, *viz.* phenol **70**. The spectral data obtained for compound **70** were in full accord with the proposed structure.* Thus, in the downfield region of the 300 MHz ^{1}H NMR spectrum of this product a doublet (J = 8.4 Hz) was observed at δ 7.16 and this is assigned to the proton at C5. The remaining downfield resonances, at δ 7.10 (d, J = 1.8 Hz) and δ 7.00 (dd, J = 8.4 and 1.8 Hz) are attributed to H2 and H4, respectively. The three-proton singlet at δ 2.46 is assigned to the methyl-group protons. The 70 eV electron impact mass spectrum of compound **70** showed a base peak at *m/z* 133, which corresponds to the expected molecular ion.

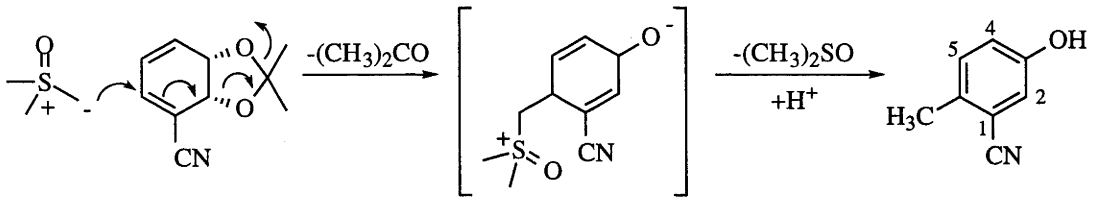
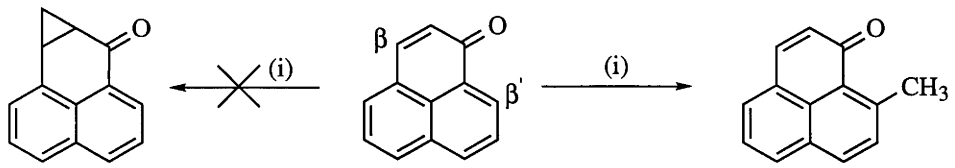


Figure 2.1: *Proposed Mechanism for the Conversion of Compound* **63** *into Phenol* **70**.

Methylation reactions of the type just described and involving dimethylsulfoxonium methylide have been observed previously.[81] For example, phenalenone **73** reacts with this ylide to give 9-methylphenalenone **74**, rather than the expected product **72** (**Scheme 2.5**).[81a] In this instance, compound **74** is obtained partly because of co-ordination of the positive-end of the ylide dipole to the carbonyl oxygen of compound **73** such that the nucleophilic end of the ylide is closer to the β'-carbon. Clearly, the formation of phenol **70** from compound **63** was of no relevance to main objectives of the work described in this thesis. The successful cyclopropanation of diene **63** with

* The synthesis of this compound has been reported previously (*Chem. Abstr.*, **1957**, *51*, 14632b), but no spectral data has been provided.

diphenylsulfonium isopropylylide but not dimethylsulfoxonium methylide might be attributed to the operation of the *gem*-dimethyl (Thorpe-Ingold) effect in the former case.[82]

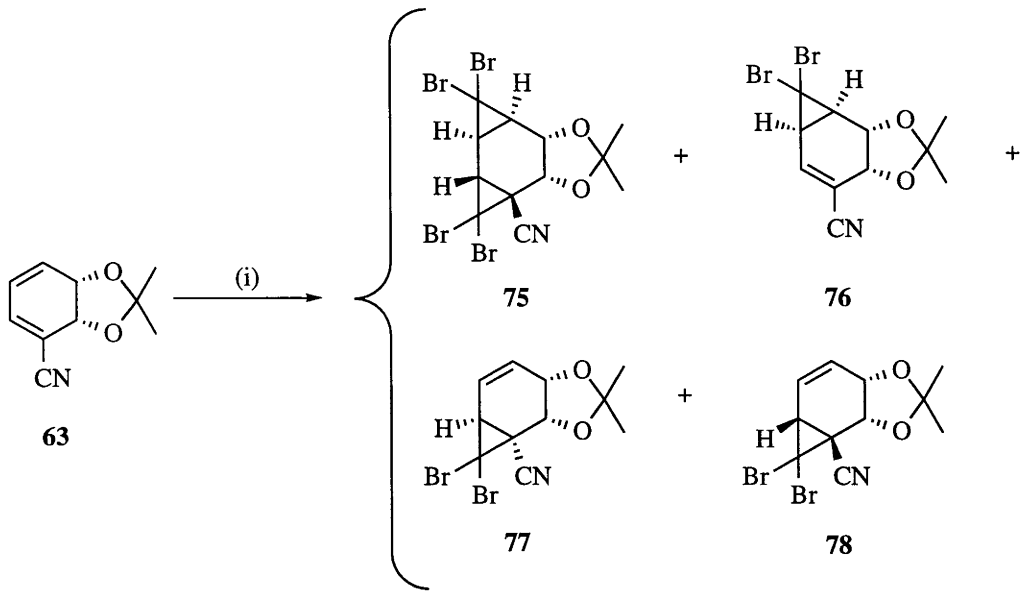


72 **73** **74**

Scheme 2.5: *Reagents and Conditions*: (i) dimethylsulfoxonium iodide (1.5 mole equiv.), NaH, DMSO, -78 °C to 0 °C, 2 h.

2.4 Attempted Electrophilic Cyclopropanation of the Benzonitrile-derived *cis*-1,2-Dihydrocatechol

Attempts to effect electrophilic cyclopropanation of compound **63** with dibromocarbene also yielded some surprises. Thus, treatment of substrate **63** with bromoform and aqueous sodium hydroxide in the presence of the phase-transfer catalyst benzyltriethylammonium chloride (TEBAC),[83] conditions frequently used to generate dibromocarbene, afforded a mixture of four adducts which could be separated from one another through a combination of fractional crystallization and chromatographic techniques (**Scheme 2.6**). In addition to obtaining significant quantities of the expected mono-adduct **76** (27%), compounds **77** (31%) and **78** (7%) together with small amounts of a single bis-adduct, **75** (5%), were also obtained.



Scheme 2.6: *Reagents and Conditions*: (i) $CHBr_3$ (5.0 mole equiv.), 50% w/v aq. NaOH, TEBAC, C_6H_6, 5 °C to 20 °C, 16 h, 70% overall yield.

Resubjection of purified mono-adduct **76** to reaction with $CHBr_3$/NaOH/TEBAC afforded, in quantitative yield, the same *bis*-adduct, **75**, as observed originally (**Scheme 2.7**), thus suggesting that the former compound is the precursor to the latter in the original reaction involving diene **63**.# Confirmation of these structures followed from a single crystal X-ray analyses as well as chemical correlation and spectroscopic studies (see below). In the 300 MHz ^{1}H NMR spectrum of the *bis*-adduct **75** (**Figure 2.2**), the doublets observed at δ 4.90 (J = 8.4 Hz) and 4.48 (J = 8.4 Hz) are assigned to the oxymethine hydrogens, H3a and H5b, respectively. In the more upfield region of the spectrum three cyclopropyl hydrogens are apparent, one of which is significantly deshielded (δ 2.75) relative to the other two (δ 2.35). This lower field resonance is assigned to the hydrogen (H4a) that is *syn*-related to the nitrile group. The remaining signals within the spectrum (two three-proton singlets at δ 1.58 and 1.39) correspond to the acetonide methyl group protons of structure **75**.

Interestingly, when compounds **77** and **78** were resubjected to reaction with $CHBr_3$/NaOH/TEBAC only the starting materials were recovered.

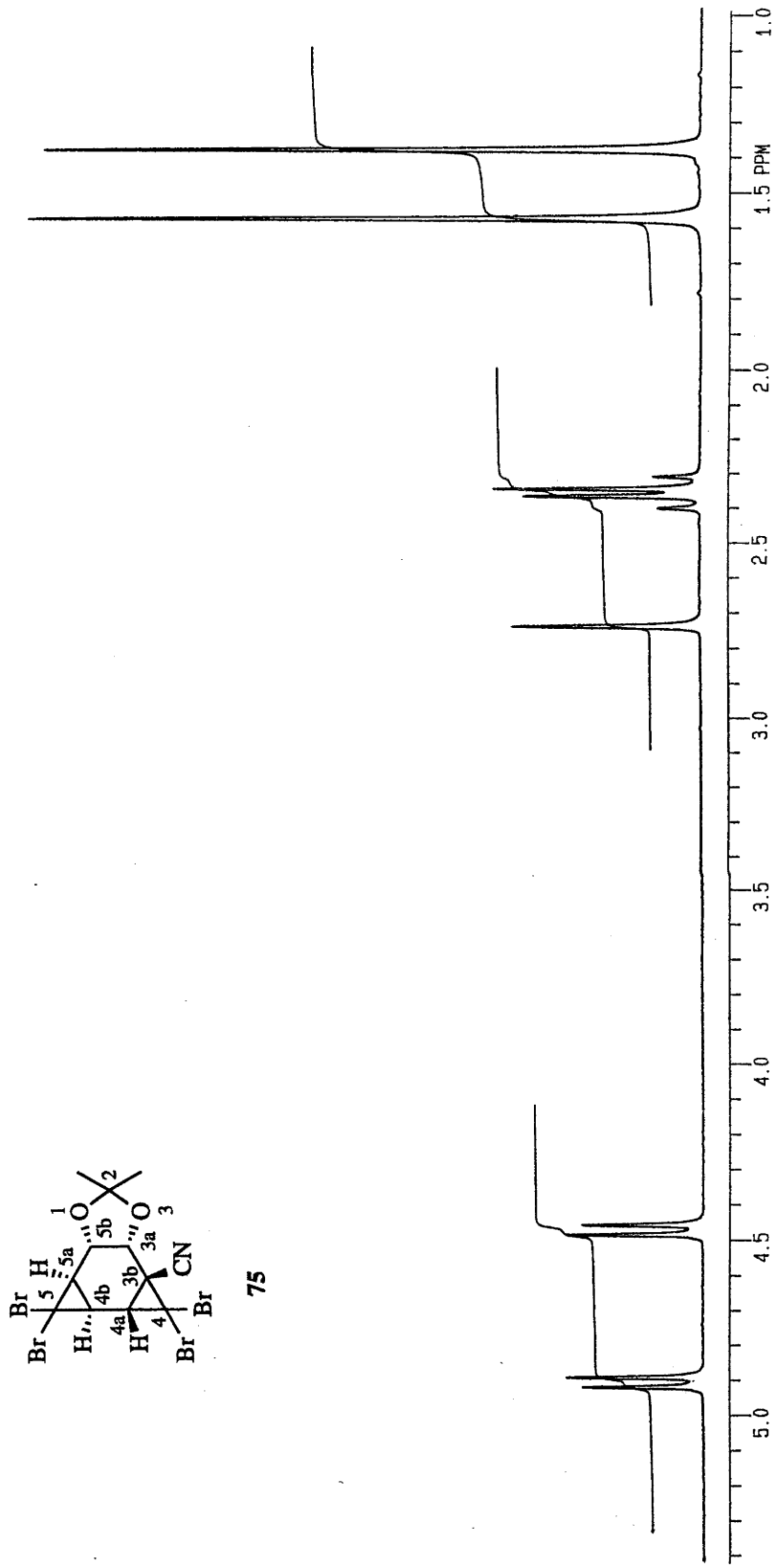
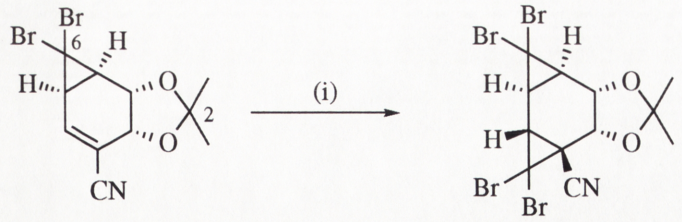


Figure 2.2: *300 MHz ^1H NMR Spectrum of Compound* **75.**
(Spectrum Recorded in $CDCl_3$ Solution)

75



76 **75**

Scheme 2.7: *Reagents and Conditions*: (i) $CHBr_3$ (10.0 mole equiv.), 50% w/v aq. NaOH, TEBAC, C_6H_6, 5 °C to 20 °C, 16 h, 98%.

Inspection of molecular models suggested that both faces of the double-bond within compound **76** are hindered [one by the *endo*-bromine at C(6) and the other by the *endo*-methyl at C(2)] and, therefore, it was not clear as to the stereochemical outcome of the dibromocarbene addition reaction leading from this compound to adduct **75**. NMR spectroscopic analysis of *bis*-adduct **75** (**Figure 2.2**) was not informative in this regard so the compound was subjected to single-crystal X-ray analysis.[84] These data (**Figure 2.3**) establish that the two cyclopropyl moieties are in an *anti*-relationship to one another. Furthermore, since it was clear (from NMR spectroscopic studies) that alkene **76** contains a trisubstituted double-bond and is the proven precursor to **75**, then this crystallographic study also provides definitive proof as to the structure of the former compound.

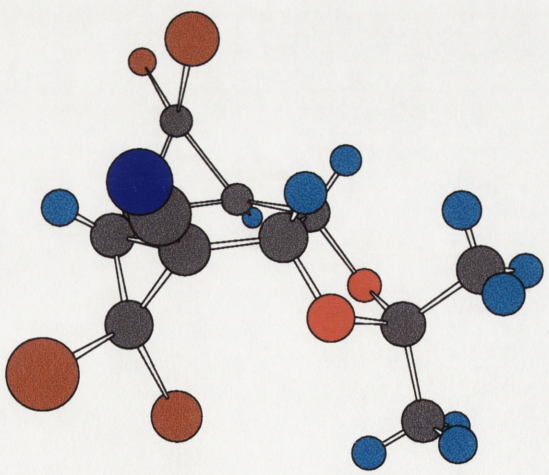


Figure 2.3: *CS Chem3D Pro™ Drawing of Compound* **75** *Generated Using Data Derived From an X-ray Crystallographic Study.*

The formation of compounds **77** and **78** in the reaction of diene **63** with $NaOH/CHBr_3$ was unexpected in that cyclopropanation of the *less* nucleophilic of the two double-bonds within this substrate has taken place under conditions that might normally have been expected to involve generation of electrophilic carbenes which are very selective for *more* nucleophilic alkenes. Consequently, it is proposed that tribromomethyl anion (which is the initially generated species in the reaction between $CHBr_3$ and NaOH) is adding in a 1,4-fashion to the Michael-acceptor **63** and the resulting conjugates, **79** or **80**, undergo a 3-*exo-tet* cyclization reaction to give the observed products (**Figure 2.4**). In other words, the unexpected products **77** and **78** do not seem so surprising if it is considered they are really likely to be products of a nucleophilic cyclopropanation reaction (albeit a rather unusual one). There is literature precedence for the 1,4-addition of the trihalomethyl anion to Michael-acceptors as a competitive process in dihalocarbene addition reactions.[85] Indeed, in some cases, it may be that the products of formal cyclopropanation derive from cyclization of the Michael addition product and not from direct carbene addition.[86]

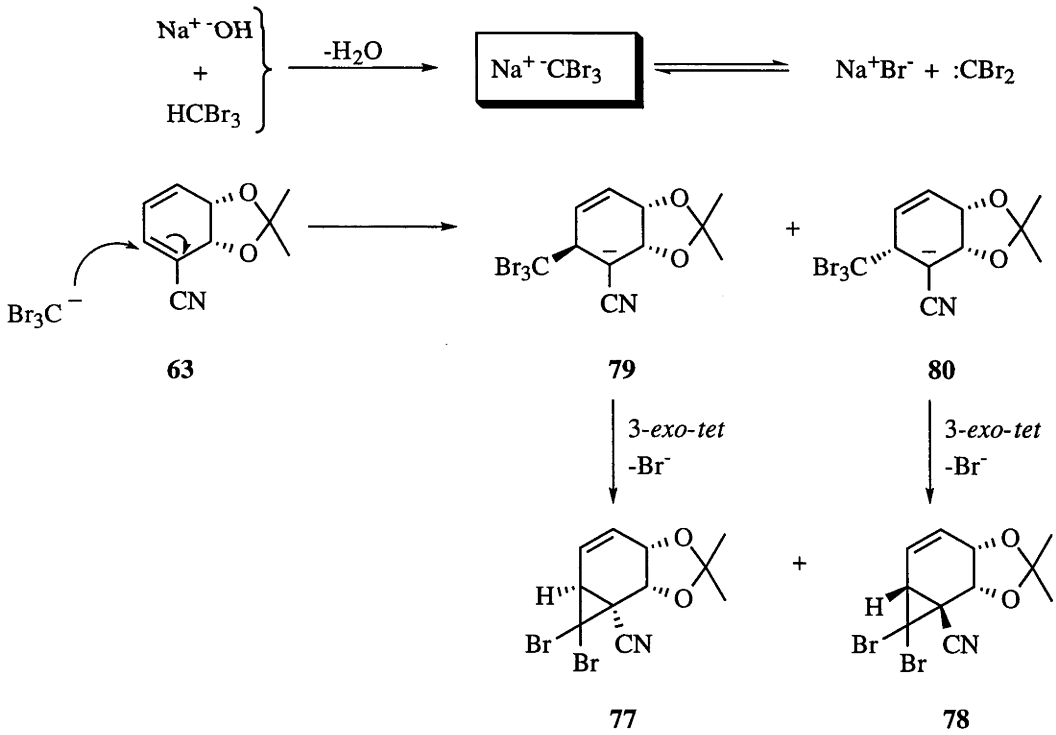
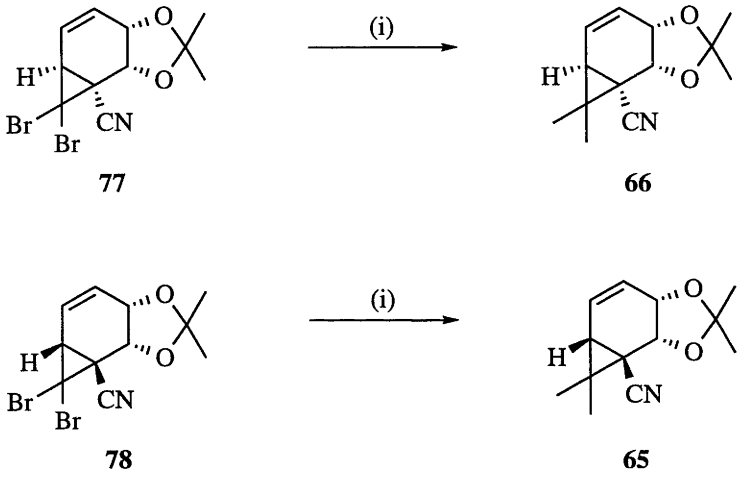


Figure 2.4: *Proposed Mechanism for the Conversion of Diene* **63** *into Products* **77** *and* **78**.

The acquisition of compounds **77** and **78** allowed for the conduct of a chemical correlation study (**Scheme 2.8**) which enabled proof of the structures of compounds **66** and **65**. Thus, reaction of each of compounds **77** and **78** with methyl iodide and the higher order cuprate $Me_2Cu(CN)Li_2$,[87] readily obtained by reaction of methyllithium with cuprous cyanide, resulted in their smooth conversion into the corresponding *gem*-dimethylated cyclopropanes **66** and **65**, compounds which had been obtained earlier while investigating the reaction of diene **63** with diphenylsulfonium isopropylidene.



Scheme 2.8: *Reagents and Conditions*: (i) CuCN (10.0 mole equiv.), MeLi (20.0 mole equiv.), MeI (36.0 mole equiv.), THF/Et_2O, -78 °C to 0 °C, 0.5 h, 85% for **66** and 78% for **65**.

Sufficient quantities of compounds **66** and **65** were available by this second route such that straightforward recrystallization of each could be carried out. This provided samples of sufficient quality for single crystal X-ray analyses of each compound (**Figure 2.5**) to be undertaken and, thereby, allowing for definitive proof of structure. These studies not only proved the stereochemical outcomes associated with the reaction between nitrile **63** and diphenylsulfonium isopropylidene, but also of compounds **77** and **78**, derived from "electrophilic" cyclopropanation of substrate **63**.

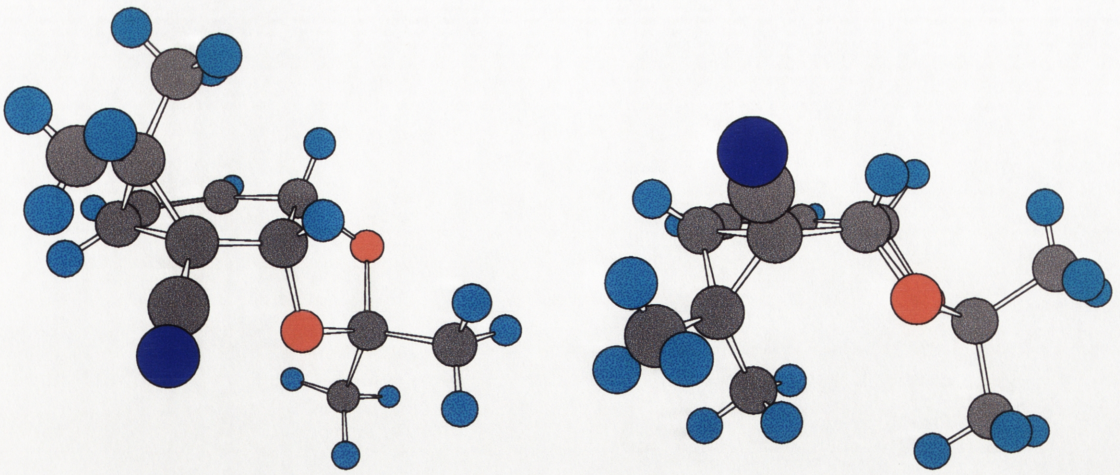
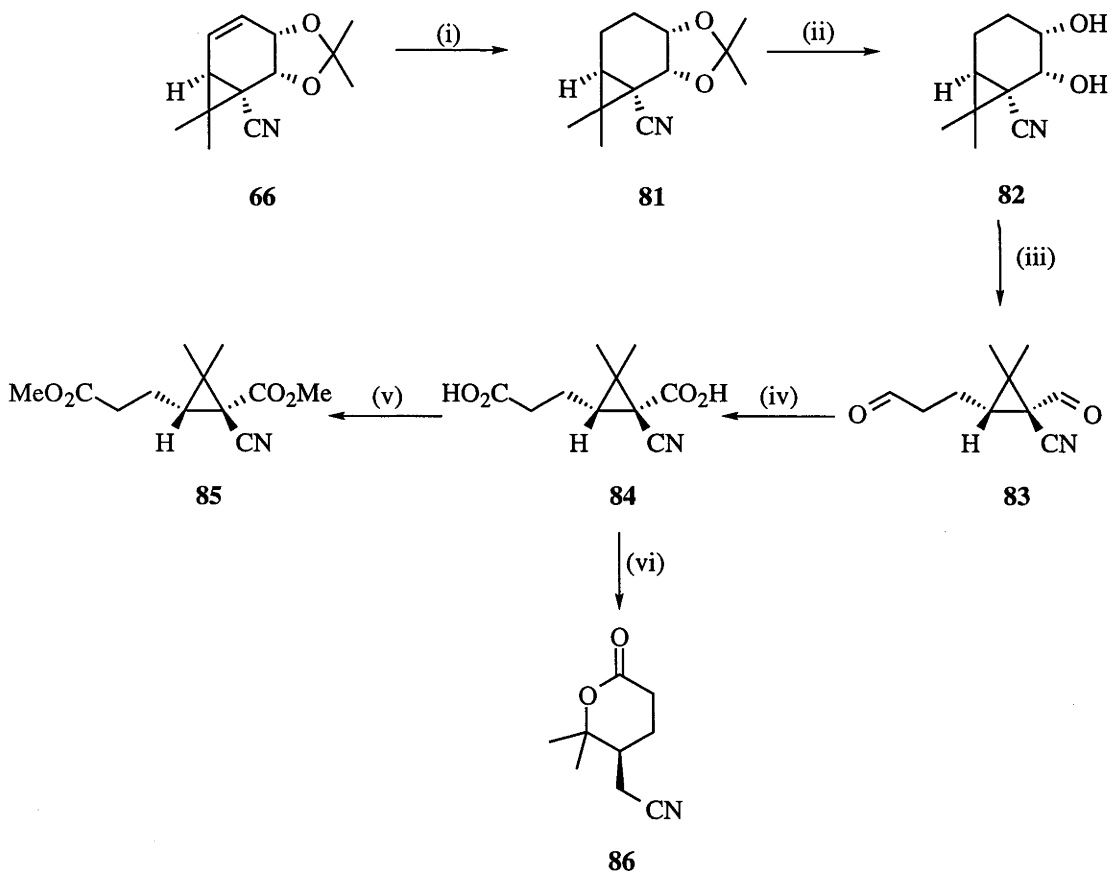


Figure 2.5: *CS Chem3D Pro™ Drawing of Compounds* **66** *(left) and* **65** *(right) Generated Using Data Derived From an X-ray Crystallographic Study.*

2.5 Synthesis of non-Ring-Fused Cyclopropanes in Enantiopure Form

A further objective of the present work was to assess the capacity of cyclopropanes such as **66** to participate in reaction sequences involving oxidative cleavage of *cis*-vicinal-diol moieties. This type of reaction should lead to open-chain cyclopropanes containing malono-half-nitrile substructures which might be expected to undergo thermally-induced decarboxylation and, thereby, allow for construction of *trans*-1,2-disubstituted cyclopropanes, structures which are ubiquitous in nature (see, for example, compounds **2**-**4** shown on page 3). In order to explore such possibilities, compound **66** was hydrogenated (**Scheme 2.9**) under standard conditions to furnish the saturated analogue **81** in 99% yield. Hydrolysis of the acetonide moiety within compound **81** using 60% aqueous acetic acid at 80 °C then afforded the *cis*-diol **82** (94%) as a white powder. Lead tetraacetate-mediated oxidative cleavage of glycol **82** provided the dialdehyde **83** (88%) as a stable oil. The spectral data obtained for the latter compound were in full accord with the proposed structure. Thus, in the downfield region of the 300 MHz ^{1}H NMR spectrum of compound **83** two singlets were observed at δ 9.76 and δ 9.58 and these are assigned to the aldehyde hydrogens present within the structure. In the aliphatic region of the spectrum the two-proton triplet at δ 2.55 and the two-proton multiplet at δ 2.05 are assigned to the methylene hydrogens

within compound **83**. The remaining signals correspond to the protons of the *gem*-dimethyl moiety (δ 1.50 and 1.38). In an effort to access structures which embody a *trans*-1,2-disubstituted cyclopropane ring, compound **83** was oxidized with silver oxide (Ag_2O) to give diacid **84**, which was characterized as the corresponding diester **85** (65% from **83**). However, efforts to effect thermally-induced decarboxylation of acid **84** in refluxing carbon tetrachloride,[88] so as to give a *trans*-1,2-disubstituted cyclopropane, were unsuccessful because of a competing lactonization to give compound **86** (56%). The spectral data obtained for this product were in full accord with the proposed structure. Thus, a ^{13}C NMR study revealed that this product contains three quaternary (C), one methine (CH), three methylene (CH_2) and two methyl (CH_3) carbons. The 70 eV electron impact mass spectrum of compound **86** showed a base peak at *m/z* 167, which corresponds to the expected molecular ion. The conversion



Scheme 2.9: *Reagents and Conditions*: (i) 10 % Pd/C, H_2, EtOH, 20 °C, 40 h, 99%. (ii) AcOH (60% aq.), 80 °C, 20 °C, 16 h, 94%. (iii) $Pb(OAc)_4$ (2.15 mole equiv.), $CaCO_3$ (12.2 mole equiv.), CH_2Cl_2, 0 °C, 0.75 h, 88%. (iv) $AgNO_3$ (5.0 mole equiv.), KOH (42.0 mole equiv.), EtOH/H_2O, 20 °C, 6 h. (v) CH_2N_2 (excess), CH_2Cl_2, 0 °C, 2 h, 65% from **83**. (vi) CCl_4, reflux, 6 h, 56%.

(**84** → **86**) most likely involves homo-Michael addition of the less-hindered carboxylic acid moiety to the *gem*-dimethylated carbon of the cyclopropane ring which cleaves to give a carbanion stabilized by both the nitrile and remaining carboxylic acid groups. After a prototropic shift within the initial cyclization product, decarboxylation ensues to give the observed lactone **86**.

In principle, by using essentially the same reaction sequence developed for the synthesis of compound **83**, its enantiomer (*ent*-**83**), should be accessible from nitrile **65**. Such chemistry would establish an enantiodivergent route to monochiral and non-ring-fused cyclopropanes from the single benzonitrile diol **63** precursor. However, because of the limitations of time, such reactions were not performed.

2.6 Summary

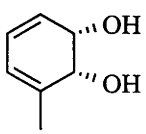
The reactions described in this chapter reveal something of the scope and limitations associated with nucleophilic and electrophilic cyclopropanation of *cis*-1,2-dihydrocatechols. They also form the basis of chemistry that has been used for the synthesis of an important pyrethroid synthon, details of which are provided in the following chapter.

CHAPTER THREE

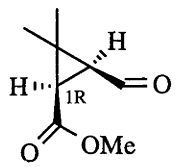
Preparation of a Key Intermediate for the Synthesis of (1*R*, *cis*)-Pyrethroids

3.1 Introduction

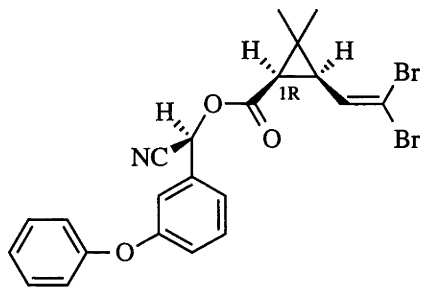
The work described in the previous chapter suggests that enantiopure *cis*-1,2-dihydrocatechols could be elaborated, *via* regio- and/or diastereo-selective cyclopropanation reactions, to various cyclopropane-containing compounds. The aim of the work described in this chapter was to examine the use of compound **17** as the starting material for the synthesis of the chiral (non-racemic) cyclopropane **87**, a key synthon associated with the production of the commercially significant (1*R*, *cis*)-pyrethroid class of insecticides such as Deltamethrine™ (**88**).



17



87



88 (Deltamethrine™)

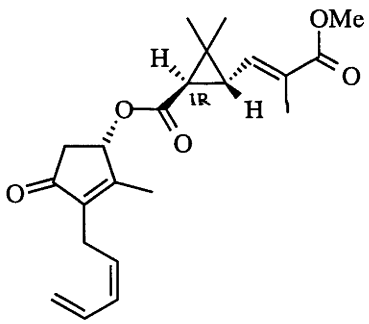
3.2 Biological and Commercial Significance of (1*R*, *cis*)-Pyrethroid Insecticides

Pyrethroids are used worldwide as insecticides in both domestic and agricultural contexts.[89,90] Pyrethrins, which are the original and natural insecticides found in certain *Chrysanthemum* species, have provided the lead compounds from which more active synthetic analogues have been developed. The commercial pyrethroids are superior to the natural ones in that only low application rates are required because the former, but not the latter, compounds exhibit high photostability. Furthermore, the commercially produced compounds have low mammalian toxicities and are biodegradable. One of the most generally successful commercial products within this group is Deltamethrine™ (**88**) which is marketed by Rhône-Poulenc Rohrer.[91]

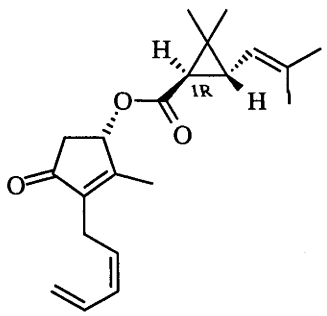
Pyrethroids are nerve-ending poisons and the precise electrophysical effects they exert are dependant upon their exact structure. Such effects can include uncoupling of

the motorneuron in the ganglion and/or repetitive back-firing of the motoraxon to the central nervous system and neuromuscular junction. Besides a whole set of structural demands, a definite range of lipophilicity is essential for the insecticidal action of pyrethroids.[89] The more polar compounds, like the naturally occurring pyrethrin II (**89**), tend to act more rapidly, at least in terms of their transient knock-down effect. Structural variations, studied over the last thirty years, have culminated in many active compounds, some of which bear, at first glance, little or no resemblance to the natural materials. However, it has recently been proposed that all active pyrethroid insecticides must be able to adopt a "horseshoe" or "clamp" conformation in the target and membrane-bound protein within the sodium-channel of the nerve ending of the insect.[89]

Many pyrethroids are sold as mixtures of all possible stereoisomers, although the one possessing the (1*R*)-stereochemistry at the cyclopropane ring usually embodies almost all of the biological activity. Only in rare instances, such as in the case of Deltamethrine™ (**88**), has the active enantiomer been marketed exclusively.



89 (pyrethrin II)



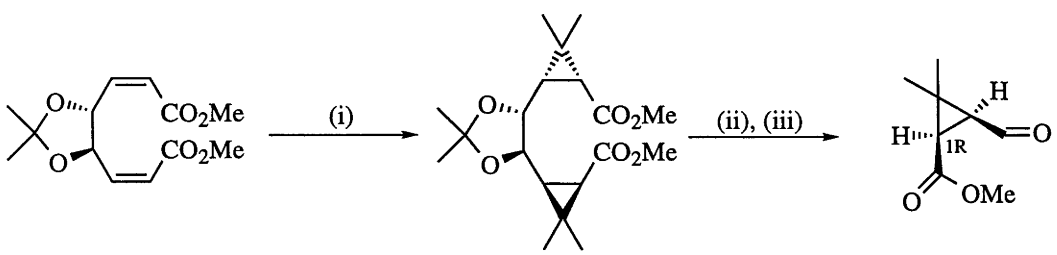
90 (pyrethrin I)

3.3 Current Methods for the Synthesis of (1*R*, *cis*)-Pyrethroid Insecticides

Worldwide, many hundreds of tonnes of pyrethroid insecticides are produced annually. The quest for higher activity and the highest possible cost/efficacy ratios has prompted great efforts by industrial and academic groups to develop ever more practical and stereoselective routes to the most active compounds. A large number of synthetic routes to chrysanthemic acid (the parent core of the pyrethroids) and its analogues have

been disclosed,[89-92] although often only in the patent literature. Most of these routes lead to a mixture of *cis*- and *trans*-diastereoisomers and only very few enantioselective syntheses of the biologically active enantiomers have been described. The latter involve the use of chirons,[93] asymmetric induction employing chiral auxiliaries,[94] chiral catalysts[95] and enzymes.[96]

The crucial *gem*-dimethyl cyclopropyl unit contained within pyrethroid insecticides can be incorporated by nucleophilic cyclopropanation techniques using a phosphonium- or a sulfonium-isopropylylide. Much of the work of this type has been carried out in Krief's laboratory over the past twenty years.[79] For example, his group has shown that by starting with cheap materials such as *L*-tartaric acid, the *bis*-γ-alkoxy-α,β-unsaturated ester **91** (**Scheme 3.1**) can be produced and then subjected to reaction with diphenylsulfonium isopropylidene. In this manner the *bis*-cyclopropanated compound **92** was obtained in an almost completely diastereoselective[79] fashion. This last compound was transformed into the desired methyl (1*R*,3*S*,*cis*)-hemicaronic aldehyde (**87**), precursor of Deltamethrine™ (**88**),[97] by hydrolysis of the 1,3-dioxolane moiety and oxidative cleavage of the resulting vicinal-diol moiety.

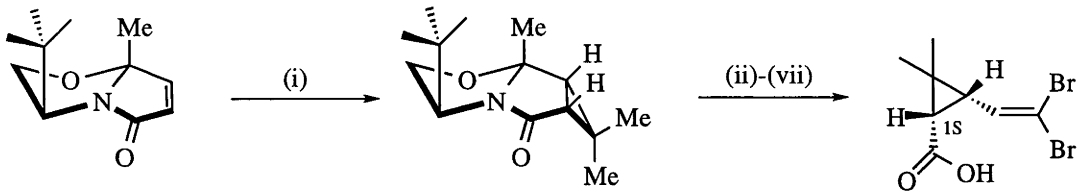


91 **92** **87**

Scheme 3.1: *Reagents and Conditions*: (i) diphenylsulfonium isopropylidene (3.0 mole equiv.), DME, -78 °C, 0.4 h then -60 °C to -50 °C, 0.6 h then -50 °C to 20 °C. (ii) 2 M $HClO_4$ (6.0 mole equiv.), THF, 20 °C, 6 h. (iii) $NaIO_4$ (1.5 mole equiv.), MeOH, pH 7.2, 20 °C, 1 h.

In an alternate approach to pyrethroids developed by A. I. Meyers at Colorado State University, cyclopropanation of chiral α,β-unsaturated bicyclic γ-lactam **93** with diphenylsulfonium isopropylidene afforded the *gem*-dimethyl cyclopropyl adduct **94** in 94% and as a single diastereomer (**Scheme 3.2**). The high levels of

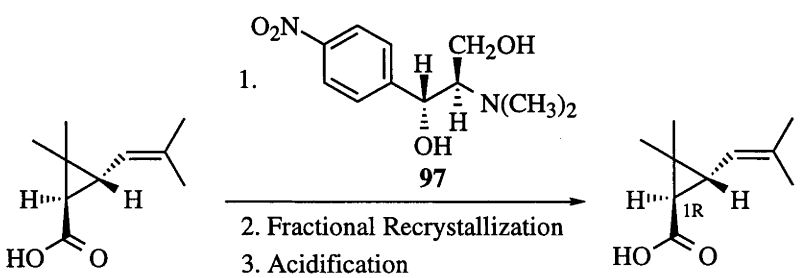
diastereoselectivity obtained in this reaction are attributed to the stereo-directing effect of the *tert*-butyl moiety present within the starting material. The chiral cyclopropane **94** was elaborated over six steps, to (-)-deltamethrinic acid (**95**), the optical antipode of the commercial material.[98]



93 **94** **95**

Scheme 3.2: *Reagents and Conditions*: (i) diphenylsulfonium isopropylidene (3.0 mole equiv.), DME, -78 °C, 0.25 h then -60 °C to -50 °C, 0.45 h then -50 °C to 20 °C. (ii) Red-Al (0.7 mole equiv.), THF, 20 °C, 12 h. (iii) $Bu_4NH_2PO_4$, CH_2Cl_2/H_2O (1:1), 20 °C, 96 h. (iv) CBr_4, PPh_3. (vii) Br_2, NaOH, -10 °C, 1 h then reflux, 1 h.

Currently, manufacture of chrysanthemate **87**, the key intermediate for the synthesis of (1*R*, *cis*)-pyrethroids, is based on ozonolytic degradation of optically active *trans*-chrysanthemic acids, which are themselves obtained by resolution of synthetically derived racemic acid.[99] Thus, treatment of *trans*-chrysanthemic acid **96** with *D*-(-)-*threo*-amine (**97**) resulted in the clean separation of the salt of the (1*R*, *trans*)-acid. Isolated by simple filtration, this salt yielded, after acidification, pure (1*R*, *trans*)-chrysanthemic acid (**Scheme 3.3**).



96 (racemic) **96** (1*R*, *trans*)

Scheme 3.3: *Commercial Method Used for the Resolution of (±)-trans-Chrysanthemic Acid* **96**.

3.4 Chemoenzymatic Route to a Key Intermediate for the Synthesis of (1*R*, *cis*)-Pyrethroids

It was envisaged that the microbially-derived *cis*-1,2-dihydrocatechol **17** could be exploited for the synthesis (in near enantiopure form) of the key pyrethroid synthon **87**. The relevant retrosynthetic analysis associated with the proposed study is outlined in **Figure 3.1**. Thus, it was anticipated that compound **87** could be derived from oxidative cleavage of the acyclic *vicinal*-diol **98** which could, in turn, be obtained *via* ozonylitic cleavage of the double bond present in the Δ^4-carene **99**.* The precursor to compound **99**, *viz.* bicycle **100**, should be available *via* diastereo- and regio-selective addition of dibromocarbene to the *bis*-TBS ether of *cis*-1,2-dihydrocatechol **17**.

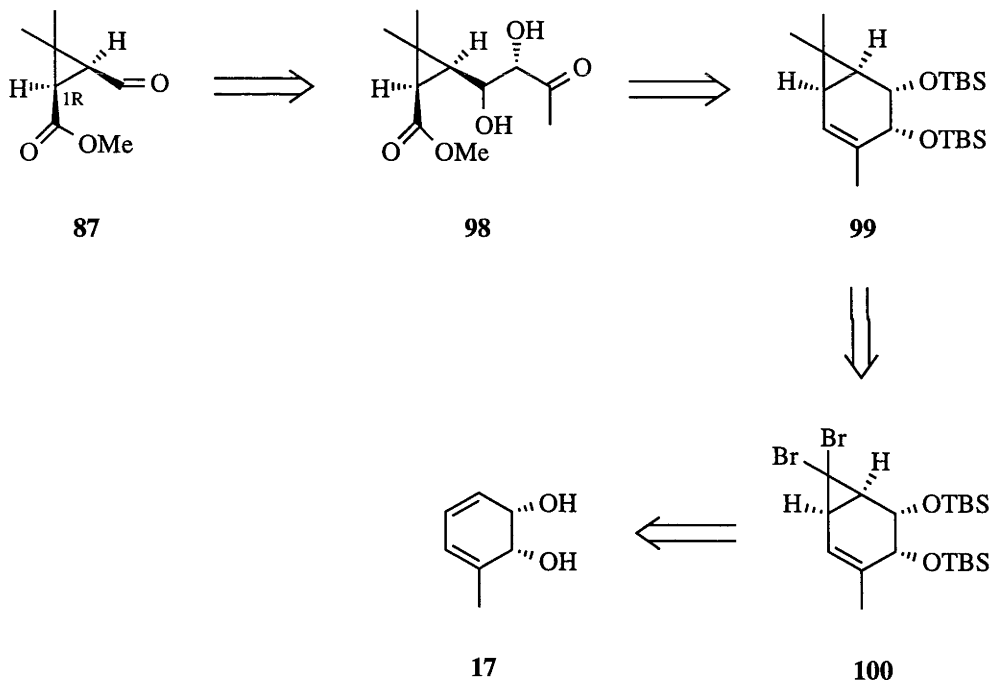


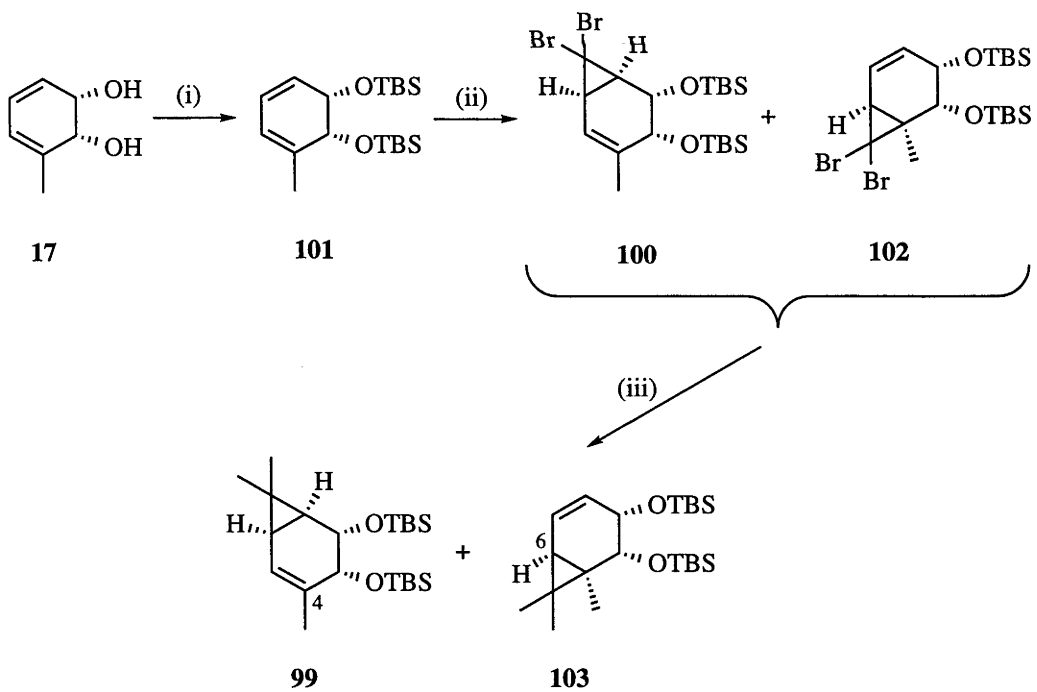
Figure 3.1: *Retrosynthetic Analysis of Pyrethroid Synthon* **87** *Based Upon Using the Toluene-Derived* cis*-1,2-Dihydrocatechol* **17** *as Starting Material.*

In the event, when the TBS-protected derivative, **101**, of the toluene-derived *cis*-1,2-dihydrocatechol **17** (**Scheme 3.4**) was reacted with dibromocarbene, an inseparable *ca.* 1:2 mixture of regioisomeric adducts, **100** and **102**, was observed. As

* Efforts aimed at effecting a related conversion of the naturally occurring Δ^3-carene into cyclopropane **87** have been reported.[100]

a consequence, this mixture of compounds was subjected to reaction, at -78 °C, with 15 molar equivalents of the higher order cuprate $Me_2Cu(CN)Li_2$ and methyl iodide. In this way the corresponding mixture of trimethylated compounds, **99** and **103**, was obtained and these products could be separated from each other by chromatography on silica gel.

In the 300 MHz ^1H NMR spectrum of compound **99**, the one-proton singlet at δ 5.39 is assigned to the olefinic hydrogen. In the more upfield region of the spectrum two oxymethine hydrogen resonances are apparent at δ 3.65 (d, J = 2.6 Hz) and 3.33 (dd, J = 5.0 and 2.6 Hz) while the resonance at δ 1.73 is assigned to the methyl group at C-4 within compound **99**. In the aliphatic region of the spectrum, the resonances at δ 1.55 and 1.14 are assigned to the two cyclopropyl protons. The hydrogens of the geminally related methyl groups attached to the cyclopropane rings resonate at δ 1.12 and 0.93, while the remaining resonances within the spectrum correspond to the TBS-ether hydrogens. The 300 MHz ^1H NMR spectrum of regioisomer **103** was rather similar save for the fact that two resonances, due to the vicinally-related olefinic



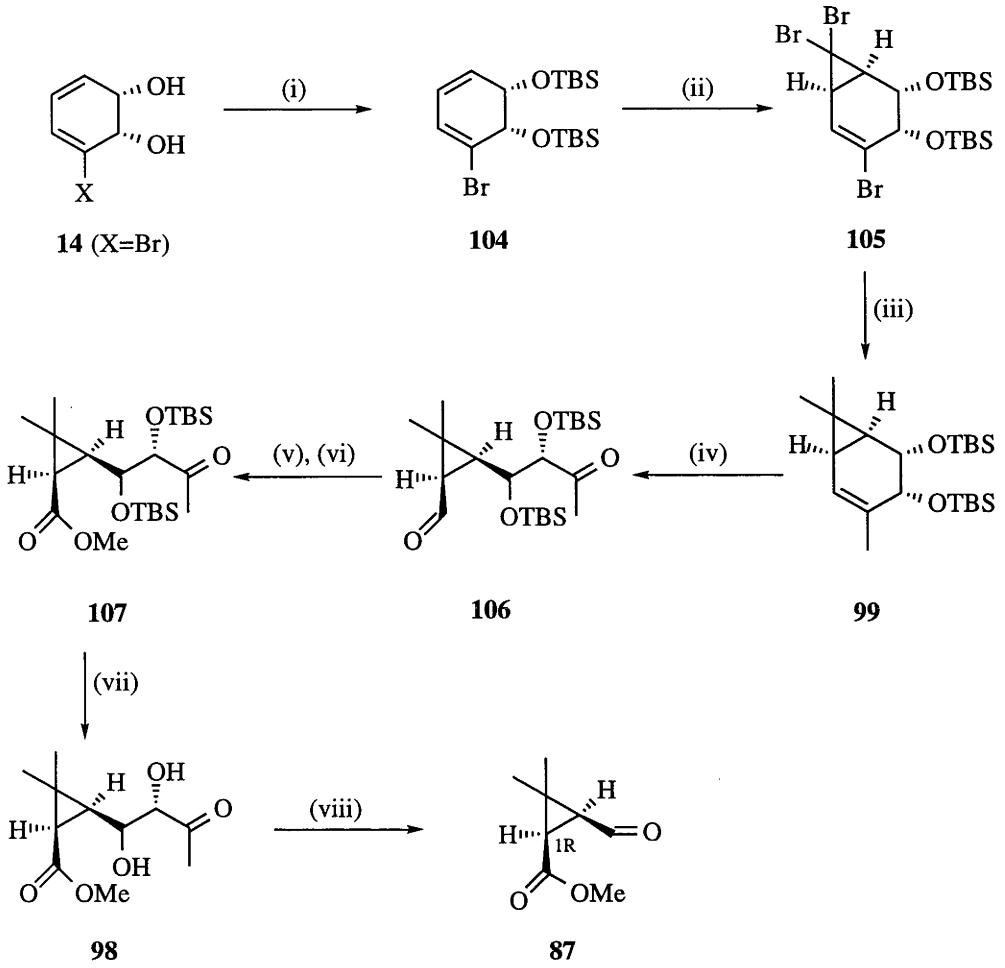
Scheme 3.4: *Reagents and Conditions*: (i) TBSCl (2.5 mole equiv.), imidazole (4.0 mole equiv.), DMF, 20 °C, 3 h, 98 %. (ii) $CHBr_3$ (5.0 mole equiv.), 50% w/v aq. NaOH, TEBAC, C_6H_6, 5 °C to 20 °C, 16 h, 68%. (iii) CuCN (10.0 mole equiv.), MeLi (20.0 mole equiv.), MeI (20.0 mole equiv.), THF/Et_2O, -78 °C to 0 °C, 0.5 h, 80%.

hydrogens, were observed at δ 5.85 and 5.72. The single cyclopropyl hydrogen (at C6) appeared at δ 1.55.

A more satisfactory means of gaining access to the key Δ^4-carene **99** is shown in **Scheme 3.5** and starts with the *bis*-(*tert*-butyldimethylsilyl) ether, **104**, of the bromobenzene-derived *cis*-1,2-dihydrocatechol **14** (X=Br). The former compound was readily obtained by reacting diol **14** (X=Br) with *tert*-butyldimethylsilyl chloride in the presence of imidazole (94%). Treatment of compound **104** with dibromocarbene, generated under phase-transfer conditions from bromoform and aqueous sodium hydroxide, then afforded the cycloadduct **105** (64%) as the only isolable product of reaction. Thus, in keeping with related conversions,[73] carbene addition occurred in a completely selective manner to the less-hindered face of the more electron-rich double-bond within diene **14** (X=Br). Compound **105** was subjected to reaction, at -78 °C, with twenty-two molar equivalents of the higher order cuprate $Me_2Cu(CN)Li_2$ and methyl iodide which resulted in formation of a trimethylated compound, **99** (70%), having spectral properties identical with those observed for the product of reaction of compound **100** with the higher order cuprate $Me_2Cu(CN)Li_2$ (**Scheme 3.4**).

Ozonolytic cleavage of the double bond within the Δ^4-carene **99**, followed by reductive work-up with dimethyl sulfide then afforded the keto-aldehyde **106**. In the 300 MHz ^{1}H NMR spectrum of this product (**Figure 3.2**) the most downfield resonance appeared as a doublet (J = 3.7 Hz) at δ 9.69 and is attributed to the aldehyde proton. The signals for the oxymethine hydrogens appeared as a one-proton doublet of doublets at δ 4.20 (J = 12.0 and 3.2 Hz) and a doublet at 3.75 (J = 3.2 Hz). The three-proton singlet at δ 2.20 is ascribed to the acetyl group protons while the cyclopropyl hydrogens resonate at δ 1.97 and 1.53. In the aliphatic region of the spectrum, the resonances at δ 1.26 and 1.25 are assigned to the hydrogens of the geminally-related cyclopropyl methyl groups. The remaining resonances correspond to the hydrogens of the TBS-ether moieties.

Attempted oxidation of compound **106** to the corresponding acid using either silver oxide (Ag_2O) or pyridinium dichromate (PDC) afforded complex mixtures of products.



Scheme 3.5: *Reagents and Conditions*: (i) TBSCl (2.5 mole equiv.), imidazole (4.0 mole equiv.), DMF, 20 °C, 3 h, 94%. (ii) $CHBr_3$ (5.0 mole equiv.), 50% w/v aq. NaOH, TEBAC, C_6H_6, 5 °C to 20 °C, 16 h, 64%. (iii) CuCN (23.0 mole equiv.), MeLi (46.0 mole equiv.), MeI (22.0 mole equiv.), THF/Et_2O, -78 °C to 0 °C, 0.5 h, 70%. (iv) O_3 (excess), CH_2Cl_2, -78 °C, 0.1 h then Me_2S (excess), -78 °C to 20 °C, 4 h, 78%. (v) $NaClO_2$ (3.0 mole equiv.), NaH_2PO_4 (1.0 mole equiv.), 2-methyl-2-butene (2.5 mole equiv.), *t*-BuOH/THF/H_2O, 0 °C, 3 h. (vi) CH_2N_2 (excess), Et_2O/CH_2Cl_2, 0 °C, 2 h, 86% from **106**. (vii) TBAF.H_2O (3.0 mole equiv.), THF, 20 °C, 3 h, 64%. (viii) $Pb(OAc)_4$ (2.1 mole equiv.), $CaCO_3$ (12.0 mole equiv.), CH_2Cl_2, 0 °C, 0.75 h, 71%.

However, Pinnick's sodium chlorite ($NaClO_2$) procedure[101] cleanly produced the desired acid which was immediately converted (using ethereal diazomethane) into the corresponding methyl ester **107** (86% from **106**). Completion of the synthesis of target **87** simply required two-fold desilylation of compound **107** followed by oxidative cleavage of the resulting open-chain diol **98**. However, the first of these conversions proved to be anything but straightforward. Ceric ammonium nitrate (CAN) is known to remove TBS-ethers as well as oxidatively cleave glycols,[102,103] so it was conceivable that the two steps just mentioned could be achieved by this one reagent.

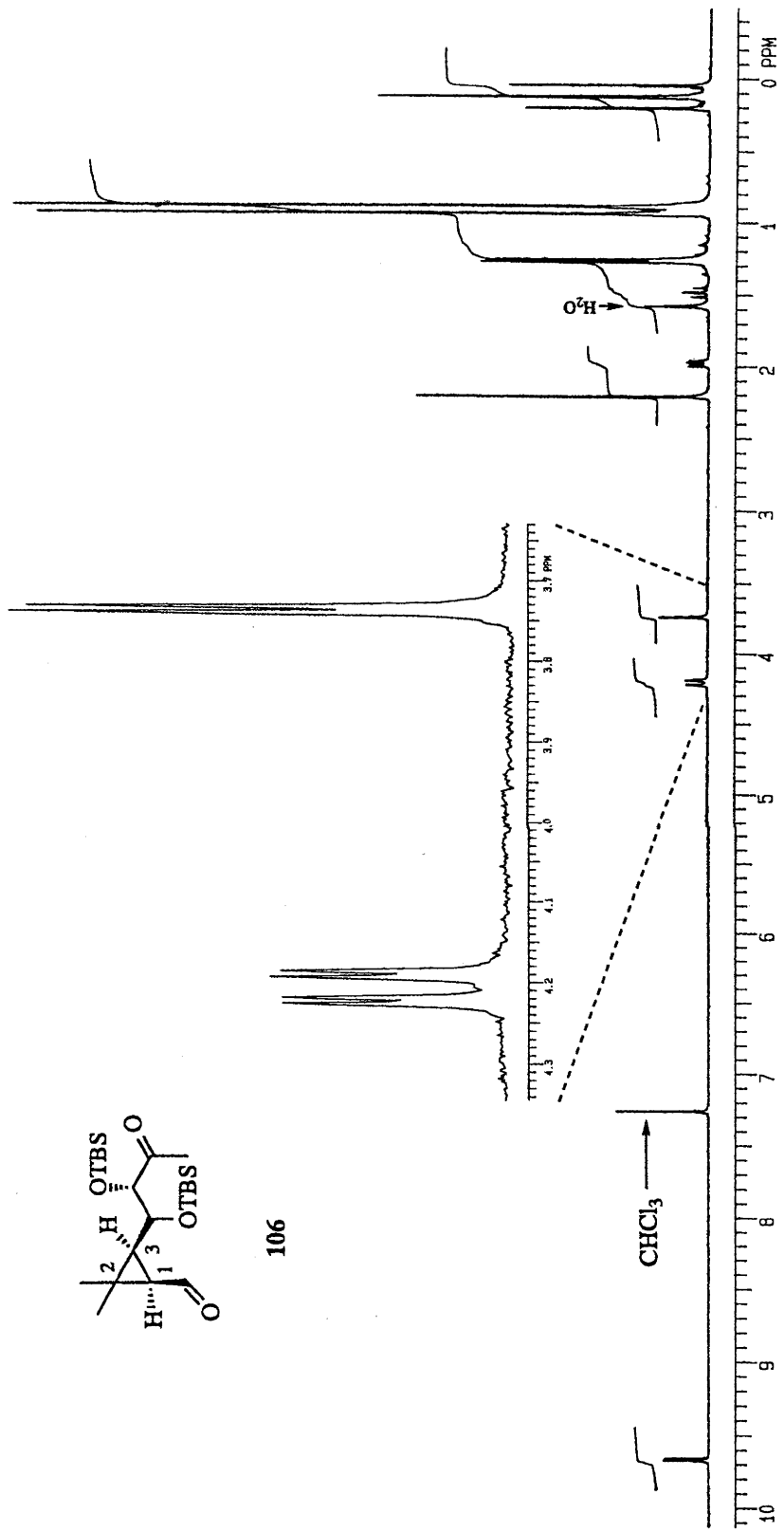


Figure 3.2: *300 MHz ^1H NMR Spectrum of Compound* **106**.
(Spectrum Recorded in $CDCl_3$ Solution)

Unfortunately, when treated with CAN, substrate **107** gave a complex mixture of products which included the target **87**, albeit in low yield. Similarly, treatment of the substrate with tetra-*n*-butylammonium fluoride (TBAF) in THF gave many products, including a trace (*ca.* 10%) of compound **87**. The formation of this latter compound under these conditions probably occurs *via* a fluoride ion-promoted retro-aldol reaction (**Figure 3.3**). Treatment of *bis*-ether **107** with HF-pyridine gave the desired diol but, even under the most favourable circumstances, in only 30% yield. Finally, it was established that treatment of the substrate with TBAF hydrate gave the desired keto-diol **98** in acceptable yield (64%). The synthesis was then completed by lead tetraacetate-promoted cleavage of diol **98** which afforded the target cyclopropane **87** in 71% yield.

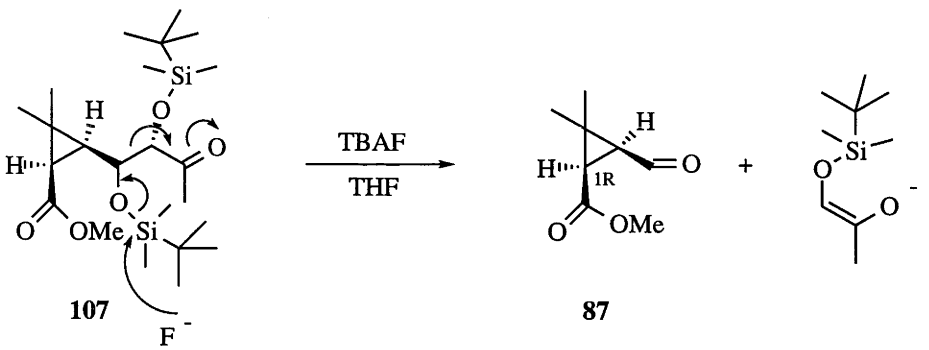
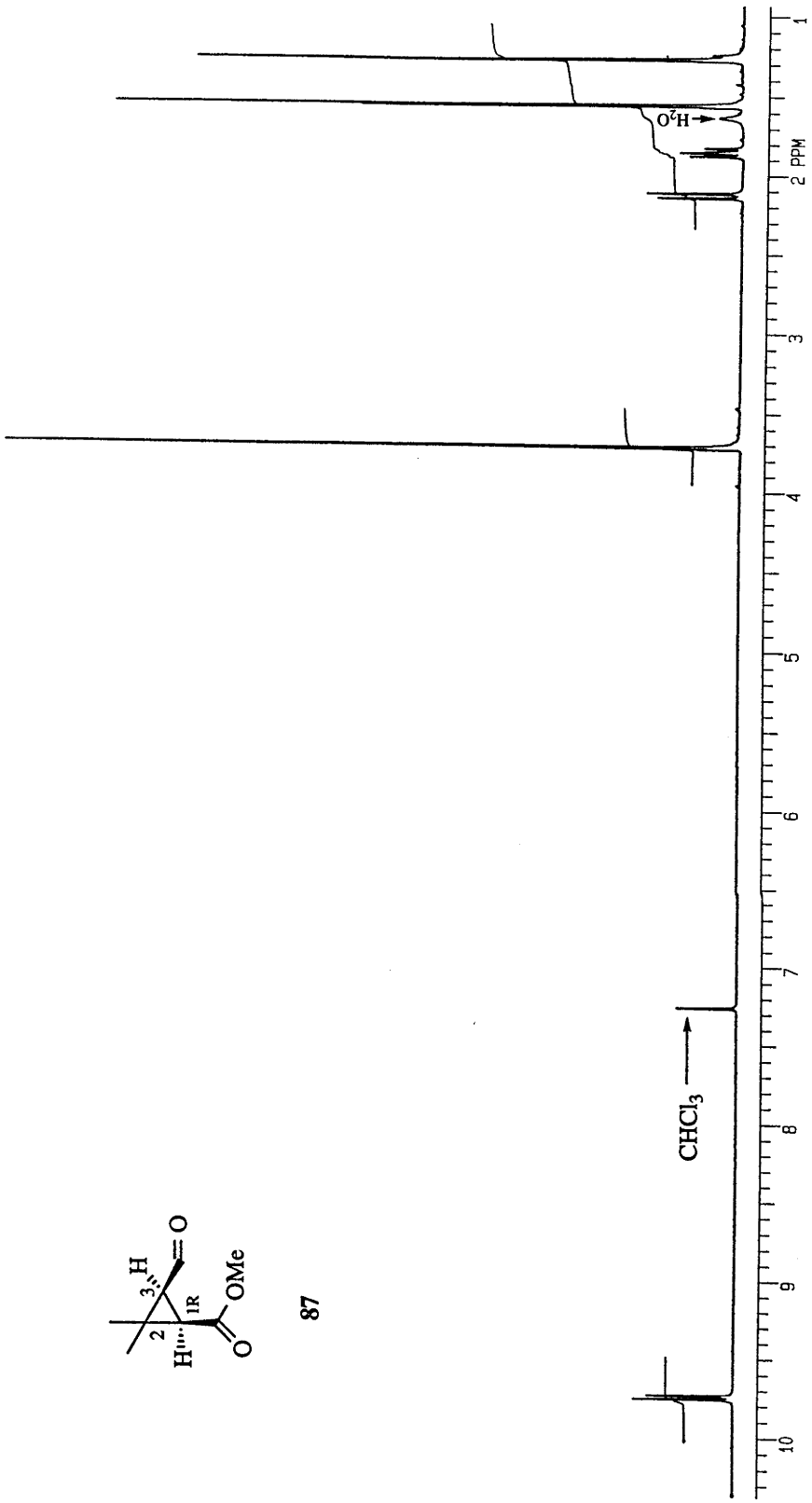


Figure 3.3: *Proposed Mechanism for the Fluoride-ion Induced Conversion of Compound* **107** *into Hemicaronic Aldehyde* **87**.

The spectral data obtained for compound **87** were in full accord with those reported previously.[104] In the downfield region of the 300 MHz ^{1}H NMR spectrum of this product (**Figure 3.4**) a doublet (J = 6.5 Hz) was observed at δ 9.76, and is assigned to the aldehyde proton. The singlet at δ 3.71 is attributed to the methyl protons of the ester group. Two one-proton cyclopropyl resonances were observed with the doublet (J = 8.0 Hz) at δ 2.14 being assigned to H1, while the (apparent) triplet (J = 8.0 Hz) at δ 1.85 is assigned to the neighbouring cyclopropyl-hydrogen, H3. The magnitude of the vicinal coupling (J = 8.0 Hz) suggests a *cis*-stereochemistry about the cyclopropane ring, as required.[104]

Two low-field resonances (at δ 200.8 and 170.7) were observed in the 75.4 MHz ^{13}C NMR spectrum of compound **87** (**Figure 3.5**) and the former signal is assigned



87

Figure 3.4: *300 MHz ^1H NMR Spectrum of Compound* **87**.
(Spectrum Recorded in $CDCl_3$ Solution)

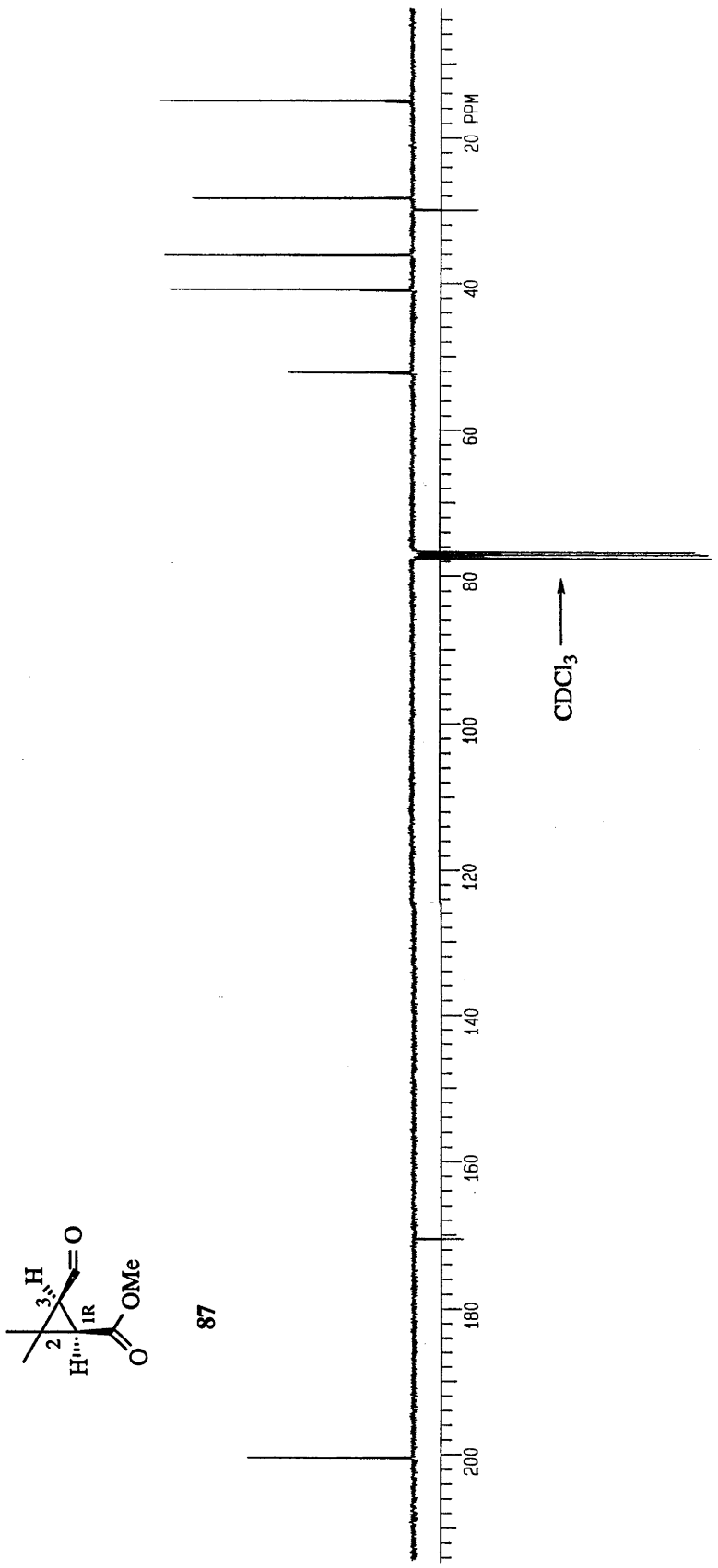


Figure 3.5: *75.4 MHz ^{13}C NMR Spectrum of Compound* **87**.
(Spectrum Recorded in $CDCl_3$ Solution)

to the aldehyde carbon, while the latter is assigned to the carbonyl carbon of the methyl ester moiety. The signal at δ 57.5 is assigned to the sp^3-hybridized carbon of the methyl ester. In the upfield region, the two signals at δ 41.1 and 36.3 are attributed to the sp^3-hybridized cyclopropyl carbons bearing hydrogens. The quaternary cyclopropyl carbon resonates at δ 30.2, while the remaining signals, at δ 28.5 and 15.2, correspond to the two methyl group carbons associated with compound **87**.

In the infrared spectrum of pyrethroid **87** two characteristic carbonyl stretching bands were observed at 1729 and 1701 cm^{-1}. The 70 eV electron impact mass spectrum of compound **87** showed a MH^+ ion at *m/z* 157 and a prominent fragment ion at *m/z* 141 which is presumably due to loss of methyl radical. The specific rotation observed for the sample of compound **87** {$[\alpha]_D^{20}$ - 55.0 ° (*c* 1.3, chloroform)} prepared by the route just described was in general agreement with reported values {e.g. $[\alpha]_D^{20}$ - 76.9 ° (*c* 17.1, acetone)[104]}.

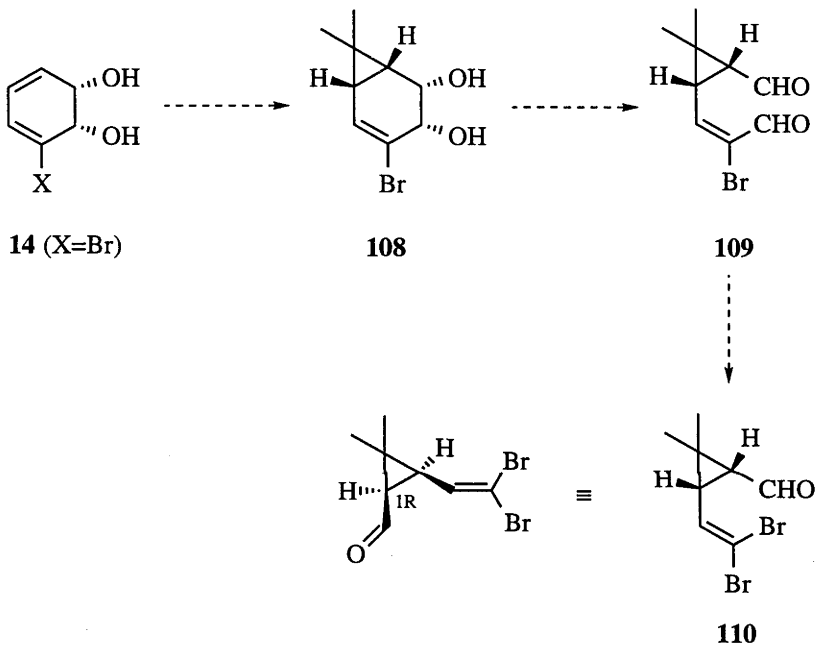
3.5 Conclusions

The microbial oxidation product **14** (X=Br) has been converted into the chiral (non-racemic) cyclopropane **87**, a key synthon for the commercially significant (1*R*, *cis*)-pyrethroid class of insecticides. The reaction sequence serves to highlight the potential utility of microbially-derived *cis*-1,2-dihydrocatechols in the preparation of monochiral cyclopropanes.[105]

While there are some attractive features to the sequence just described there is definitely room for improvement especially in respect to the matter of atom economy. Thus, as the synthesis of compound **87** stands at present only four of the carbon atoms present in *cis*-1,2-dihydrocatechol **14** (X=Br) are carried through to the target. This situation could be improved dramatically if it were possible to effect diastereofacially selective *gem*-dimethylcyclopropanation of starting material **14** (X=Br) such that this reaction occurred from the α-face (**Scheme 3.6**). The product of the reaction, *viz.* compound **108**, could then be subjected to oxidative cleavage of the *cis-vicinal*-diol moiety so as to produce dialdehyde **109**, which through brominative

decarbonylation[106] of the allylic aldehyde group might be converted into the Deltamethrine™ precursor **110**.

Of course, the greatest challenge associated with implementing such ideas involves achieving the pivotal cyclopropanation reaction [*viz.* **14** (X=Br) → **108**] in a diastereo- and regio-selective manner. Our present state of knowledge concerning the cyclopropanation of *cis*-1,2-dihydrocatechols does not suggest an obvious way of achieving this. Nevertheless, such important objectives are being pursued by other members of this laboratory.



14 (X=Br) **108** **109** **110**

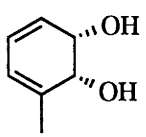
Scheme 3.6

CHAPTER FOUR

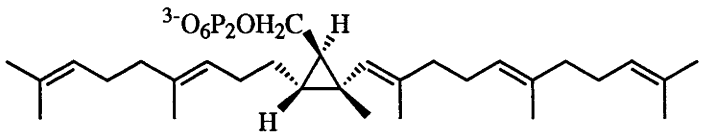
Chemoenzymatic Synthesis of Presqualene Diphosphate Analogues

4.1 Overview

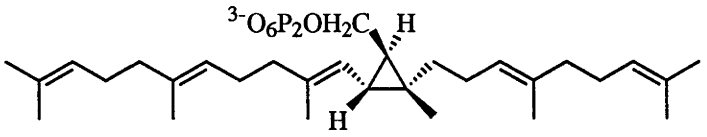
In the preceeding chapter a means for converting *cis*-1,2-dihydrocatechol **14** (X=Br) into a key intermediate, **87**, associated with the synthesis of commercially significant pyrethroid insecticides was described. The aim of the work described in this chapter was to use *cis*-1,2-dihydrocatechol **17** as the starting material for the synthesis of the chiral (non-racemic) cyclopropane **111**, which, by virtue of it being a structural analogue of presqualene diphosphate **112** (PSDP), was expected to be a potential inhibitor of cholesterol biosynthesis. The difference between the target compound **111** and the natural product **112** is that the positions of the side-chains have been interchanged. As such, compound **111** should be recognized by the relevant enzyme systems but not be able to be processed by them.



17



111



112 (presqualene diphosphate, PSDP)

4.2 Biological Properties of Presqualene Diphosphate

An important means for reducing the concentration of low-density lipoprotein cholesterol (LDL-C) in blood plasma, a key risk factor in coronary heart disease, is to inhibit cholesterol biosynthesis.[107,108] The biosynthesis of cholesterol comprises some twenty-six reaction steps, and these are summarized in **Figure 4.1**. A number of therapeutic agents for the treatment of elevated LDL-C levels are presently available and these act to reduce levels of mevalonic acids by inhibiting hydroxymethylglutaryl-CoA (HMG-CoA) reductase.[109] This desirable effect on plasma LDL-C is a consequence of

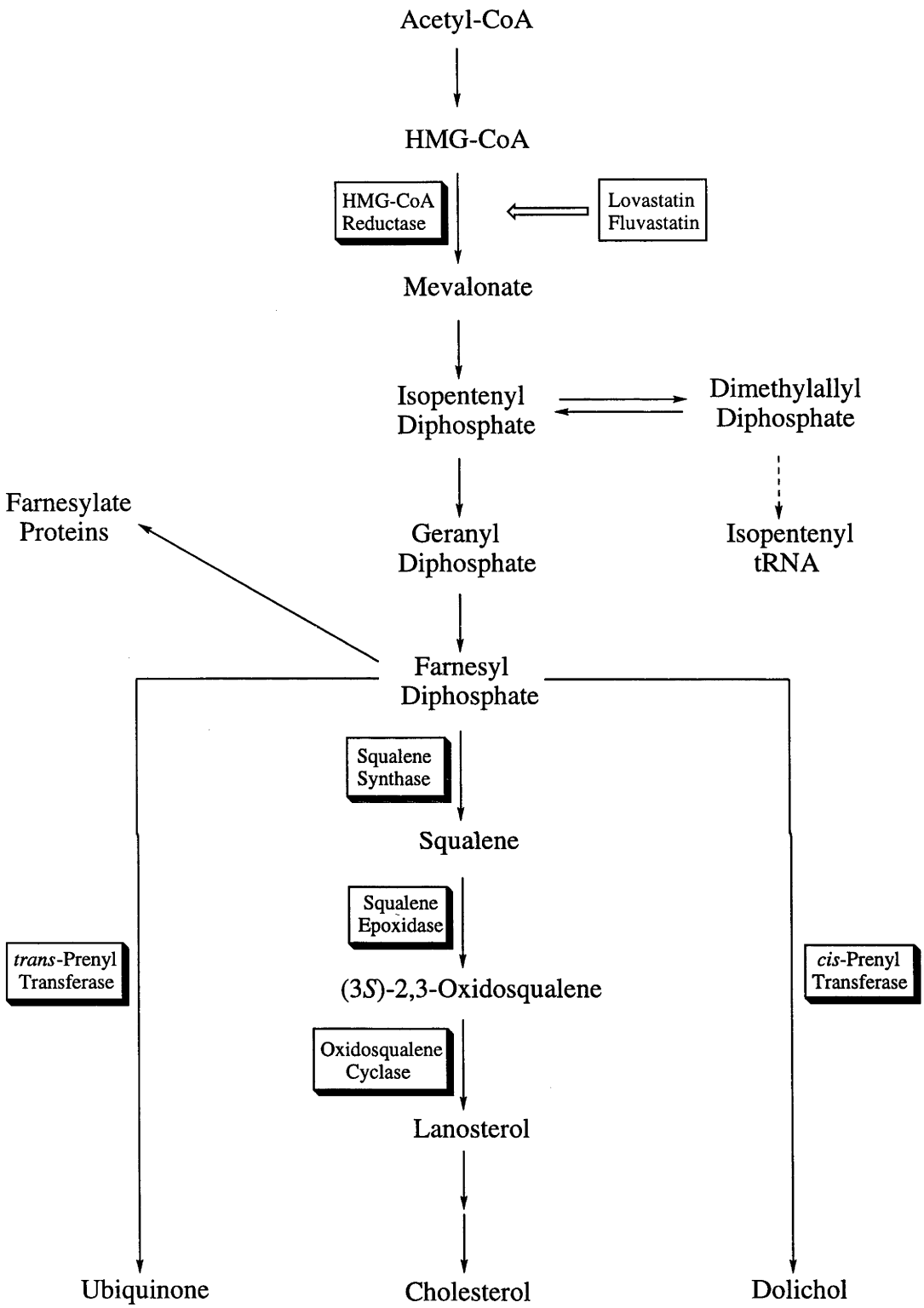


Figure 4.1: *Biosynthetic Pathway Associated with the Production of Cholesterol and Biogenetically Related Compounds.*

inhibition of cholesterol biosynthesis in the liver, leading to the upregulation of the LDL receptor. However, mevalonate is an important precursor for non-steroidal isoprenoids such as dolichol, ubiquinone and isopentenyl tRNA. It is also required for production of farnesyl diphosphate and geranylgeranyl diphosphate, the terpenoid compounds necessary in protein prenylation (**Figure 4.1**).[110-112] Clearly, then, inhibition of the biosynthesis of mevalonic acid will have some undesirable side-effects. The concerns raised by such matters have prompted many researchers to focus their efforts on the development of inhibitors of cholesterol biosynthesis that act at alternate (especially later) points on the pathway. One of these is the first committed step in the biosynthesis of cholesterol, which is catalyzed by squalene synthase (SQS).[113-119] Thus, this enzyme effects the 1'-1 coupling[120] of farnesyl diphosphate **113** so as to produce the triterpene squalene **114** *via* the intermediate cyclopropane presqualene diphosphate (PSDP, **112**, **Figure 4.2**).[121] It is thought that PSDP (**112**) rearranges to squalene **114** by a series of steps that involve loss of inorganic pyrophosphate (PP_i), rearrangement of the hydrocarbon skeleton and incorporation of hydrogen from nicotinamide adenine dinucleotide phosphate hydride (NADPH).[122] A key feature of the pathway associated with this transformation is the likely involvement of a tertiary cyclopropylcarbinyl cationic intermediate **115** (**Figure 4.3**).[123] Because of its key position in the biosynthetic pathway, squalene synthase is an attractive target for the development of pharmacological drugs to reduce serum cholesterol levels. Presumably inhibition of this enzyme would not lower levels of important non-steroidal isoprenoids in the cell.

Interestingly, very recently PSDP has been shown to act as a potent signalling agent that regulates oxygen-radical formation in neutrophils, a key response in microbial killing, inflammation and tissue injury.[124] On the basis of the foregoing, it would seem that PSDP analogues could be very important compounds from a biological standpoint.

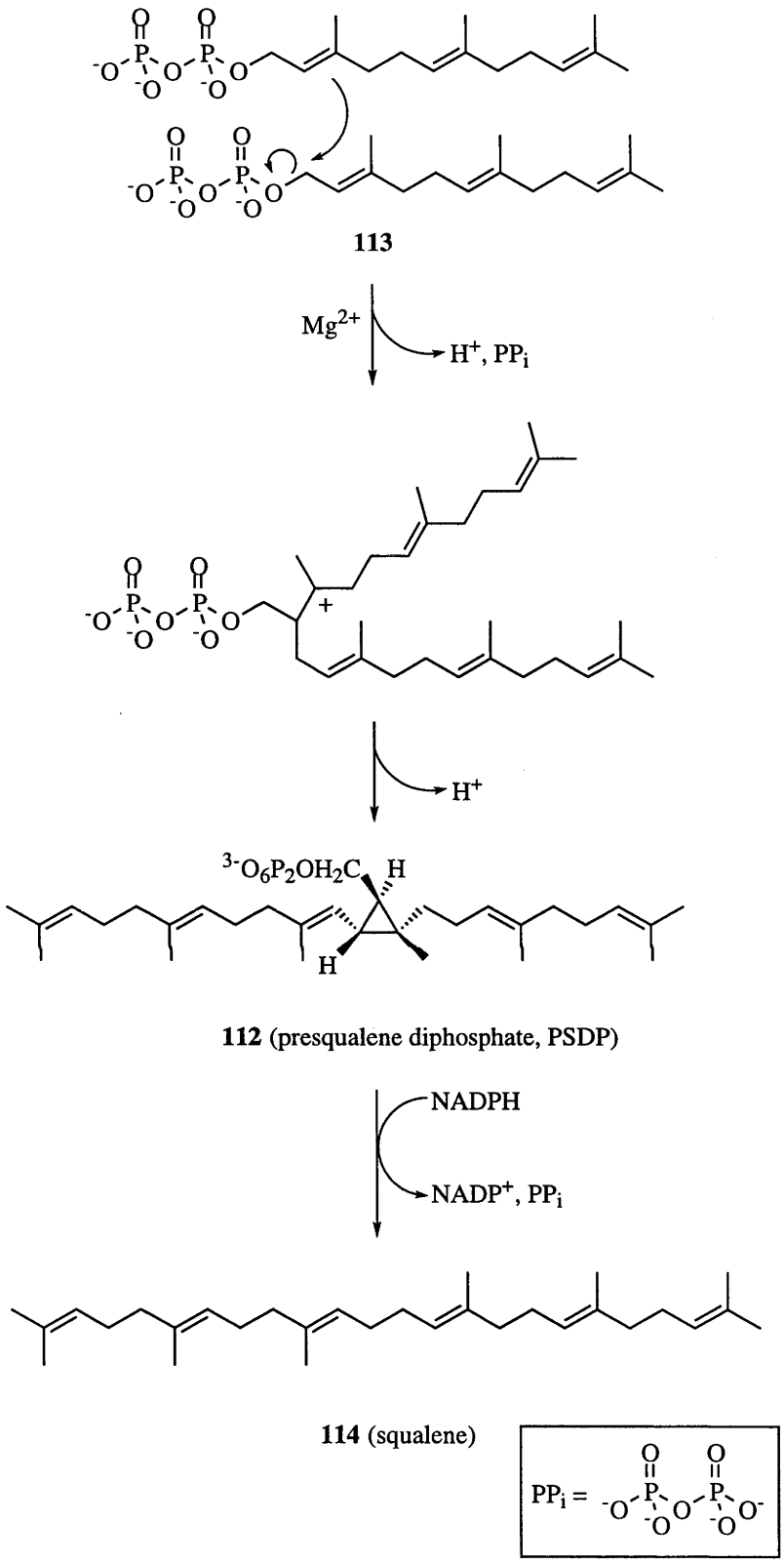


Figure 4.2: *Biosynthesis of Squalene* (**114**) *from Farnesyl Diphosphate* (**113**).

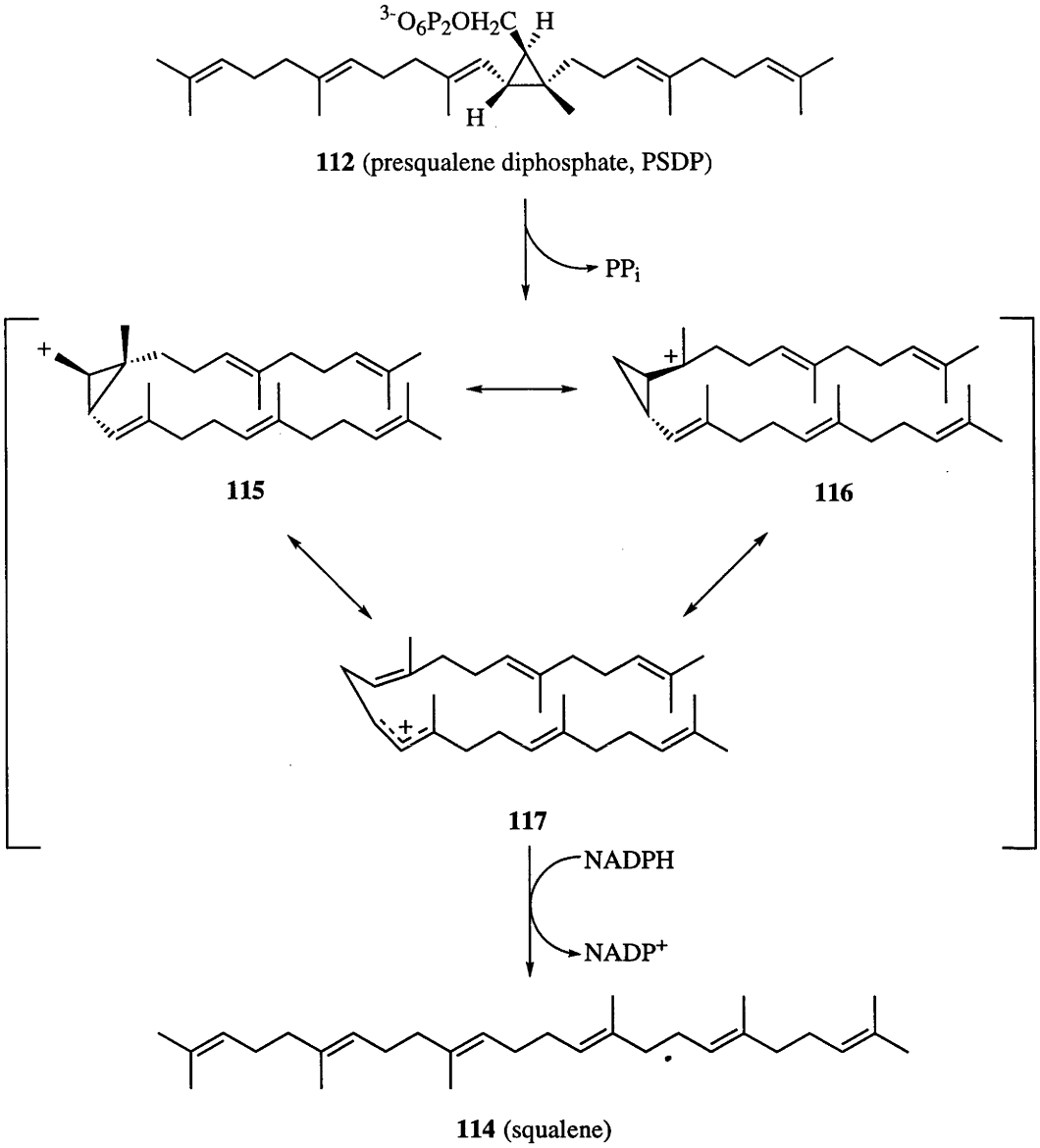
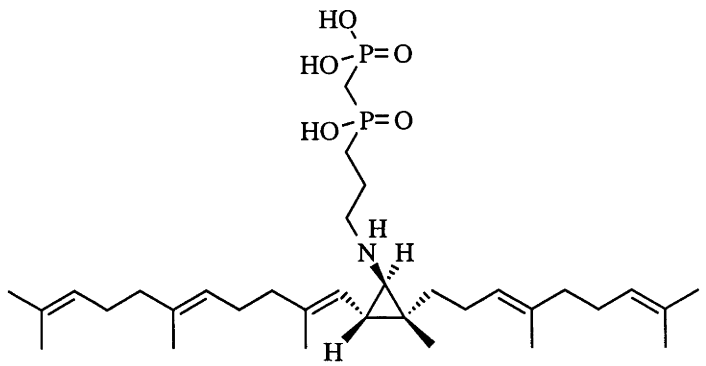


Figure 4.3: *Putative Carbocationic Intermediates* **115-117** *Involved in the Conversion of Presqualene Diphosphate* (**112**) *into Squalene* (**114**).

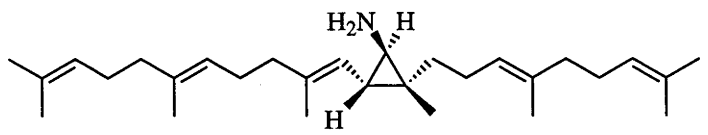
4.3 Squalene Synthase (SQS) Inhibitors

Notable progress has been made in the development of PSDP analogues capable of inhibiting squalene biosynthesis and metabolism.[125] For example, many stable analogues of farnesyl diphosphate have been synthesized, and a good proportion of these are inhibitors of SQS. Analogues of PSDP that mimic its reductive rearrangement to squalene have also been developed. Thus, compounds **118-120** (**Figure 4.4**) were

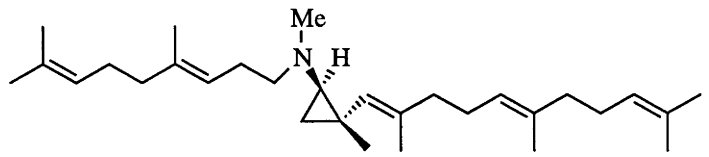
all designed to mimic the carbocationic species **115-117** and, indeed, in the presence of added inorganic diphosphate (PP_i), they proved to be good inhibitors of SQS.[126,127]



118



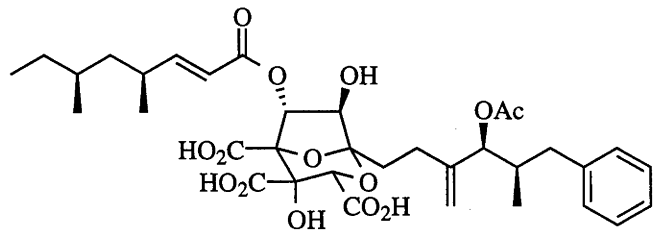
119



120

Figure 4.4: *Analogues of PSDP that Inhibit Squalene Synthase (SQS).*

The screening of fermentation cultures for natural products that inhibit SQS has also proven fruitful. Several novel fungal metabolites that act as potent inhibitors have been discovered with, perhaps, the most notable examples being squalestatins 1 [a.k.a. zaragozic acid A (**121**)], 2 and 3.[128-130]



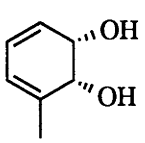
zaragozic acid A / squalestatin 1 (**121**)

4.4 Methods for the Synthesis of Presqualene Diphosphate

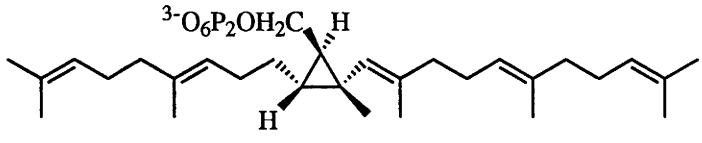
Several syntheses of racemic presqualene alcohol, the necessary precursor to PSDP, have been reported,[131-133] including one where the required alcohol was obtained in enantiomerically pure form *via* resolution of the racemate.[134] However, only one enantioselective synthesis of (+)-presqualene alcohol has been described to date.[135] Thus, the natural, (1*R*,2*R*,3*R*), enantiomer of PSDP (**112**) was synthesized from farnesol in greater than 98% ee by Poulter *et al.* (**Scheme 4.1**). The key step was an intramolecular and enantioselective cyclopropanation of farnesyl diazoacetate (**122**) which was catalyzed by treatment of this compound with the chiral rhodium catalyst (Rh_2[5(*R*)-MEPY]$_4$) and provided the lactone **123** in greater than 94% enantiomeric excess. Standard manipulation of compound **123** afforded aldehyde **124** which was then elaborated, in a straightforward manner, to PSDP (**112**).[135]

4.5 Design of a Potential Squalene Synthase Inhibitor

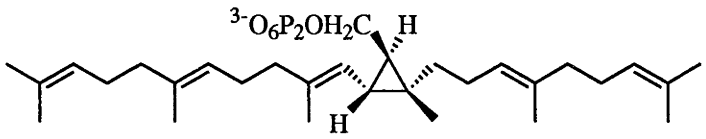
On the basis of the foregoing, it was envisaged that cyclopropane **111** could act as a potent inhibitor of SQS and, hence, the biosynthesis of cholesterol. This proposal was based on the idea that a structurally related analogue of PSDP such as compound **111**, which has the same overall carbon-chain length and stereochemistry (about the central cyclopropane unit) as the natural substrate **112**, would be recognised by the SQS



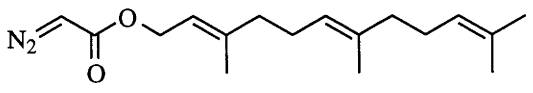
17



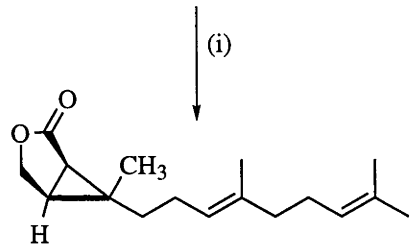
111



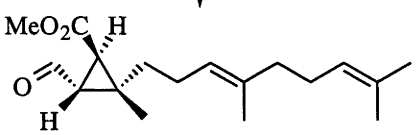
112 (presqualene diphosphate, PSDP)



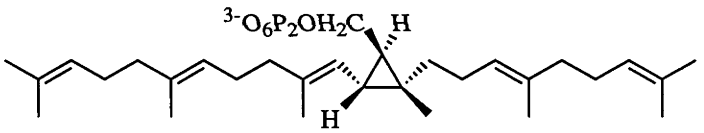
122



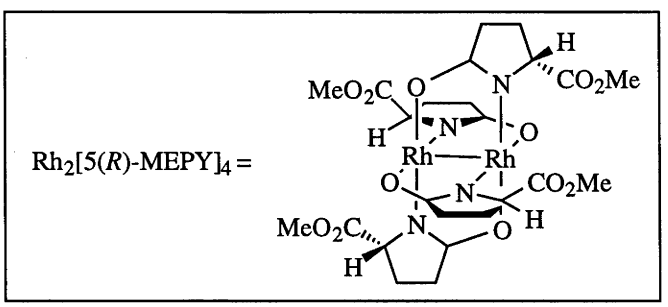
123



124



112 (presqualene diphosphate, PSDP)



Scheme 4.1: *Reagents and Conditions*: (i) $Rh_2[5(R)\text{-MEPY}]_4$, CH_2Cl_2, reflux, 96%. (ii) NaOH, MeOH, 21 h. (iii) CH_2N_2 (excess), 0 °C, 0.1 h. (iv) NMO , 4Å molecular sieves, TPAP (0.05 mole equiv.), CH_2Cl_2, 20 °C, 0.5 h, 79% from **123**. (v) NaOH, MeOH, 25 h, 20 °C, 85%. (vii) [(*E*)-5,9-dimethyl-deca-4,8-dien]triphenylphosphonium iodide, *n*-BuLi, THF, 0 °C, 0.25 h then MeI, 0.25 h then *n*-BuLi, 0.25 h. 53%. (viii) $LiAlH_4$, Et_2O, 0 °C, 3 h, 96%. (ix) $(n\text{-}Bu_4N)H_2PO_4$, CCl_3CN, CH_3CN, 20 °C, 1 h. (x) $(PhO)_2POCl$, Bu_3N, $(n\text{-}Bu_4N)H_2PO_4$, C_6H_5N, 20 °C, 5 h. (19% over 2 steps).

enzyme. However, by virtue of the position of the cyclopropane moiety within this structure, the compound should not be capable of being processed by the enzyme (or, at least, not processed in the "normal" way) and would, therefore, act as an inhibitor of it. Interestingly, the subtle structural modification associated with analogue **111** swaps the longer-farnesyl (left-hand) side-chain in PSDP **112** with the shorter-geranyl aliphatic side-chain. Likewise, the shorter-geranyl (right-hand) side-chain present within PSDP **112** replaces the longer-farnesyl side-chain in compound **111**. In other words, the two side-chains attached to the central cyclopropane ring have been interchanged. It was anticipated that *cis*-1,2-dihydrocatechol **17**, obtained from microbial oxidation of toluene, could be utilized in the synthesis of this very interesting target compound **111**.

4.6 Synthesis of Structural Analogues of Presqualene Alcohol

The relevant disconnections associated with the proposed synthesis of target **111** from *cis*-1,2-dihydrocatechol **17** are outlined in **Figure 4.5**. Thus, in the synthetic direction, Wittig olefination of compound **125** would provide compound **111**. It was expected that aldehyde **125** could, in turn, be derived from selective Wittig olefination of the sterically more accessible carbonyl moiety present within dialdehyde **126**. Dialdehyde **126** should be accessible *via* oxidative cleavage of diol **127**, which would be obtained *via* straightforward manipulation of acetonide **128**, the 2,3-dihydro-analogue of toluene-derived diol **17**. Furthermore, manipulation of the readily available 1-bromo-3-methyl-2-butene (**130**) and geranyl bromide (**132**) by known protocols should provide the necessary precursors, **129** and **131**, respectively, to the ylides required for the aforementioned Wittig olefination reactions.[136]

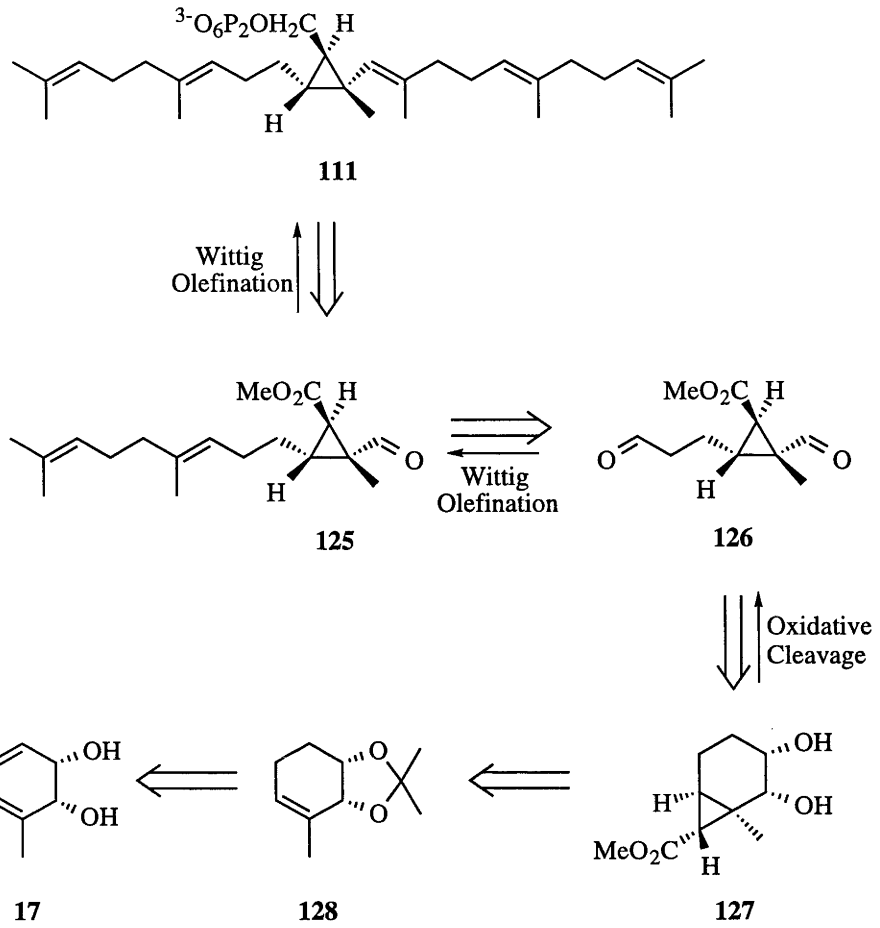
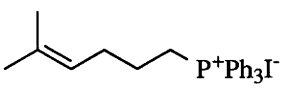
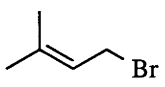


Figure 4.5: *Retrosynthetic Analysis of PSDP Analogue* **111** *Based Upon Using the Toluene-Derived* cis-*1,2-Dihydrocatechol* **17** *as Starting Material.*

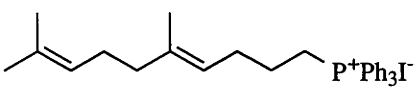
In reality, the synthetic sequence began (**Scheme 4.2**) with selective reduction of the less-substituted double-bond present in *cis*-1,2-dihydrocatechol **17**. This conversion was effected with diimide[137] and afforded the previously reported ene-diol **133** as a white crystalline solid in 83% yield. The spectral data obtained on this latter



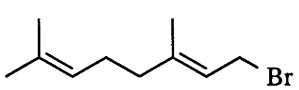
129



130

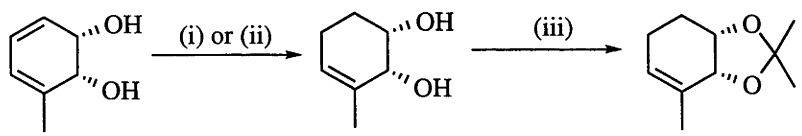


131



132

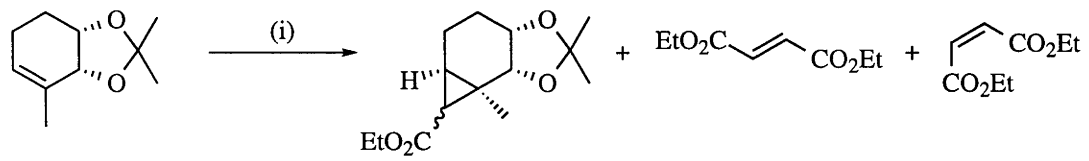
compound were in full accord with those previously reported by Hudlicky *et al.*[138] Another method for preparing compound **133** involved catalytic hydrogenation of diene **17** using 5% rhodium supported on alumina. Although both procedures for effecting the conversion (**17**) → (**133**) were high yielding, the latter was more amenable to large-scale synthesis and, thus, represented the method of choice. Protection of the diol unit present within compound **133** as the corresponding acetonide was readily achieved by reaction with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid monohydrate (**Scheme 4.2**) and in this manner derivative **128** was obtained in 94% yield.



17 **133** **128**

Scheme 4.2: *Reagents and Conditions*: (i) dipotassium azodicarboxylate (7.0 mole equiv.), AcOH (14.5 mole equiv.), MeOH, 20 °C, 0.75 h, 83%. (ii) 5% Rh/Al_2O_3, H_2, EtOH, 20 °C, 16 h, 96%. (iii) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (0.05 mole equiv.), 0 °C, 1 h, 94%.

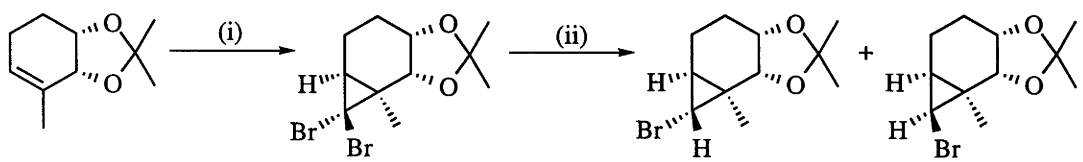
The task of modifying alkene **128** so as to provide access to the key cyclopropyl compound **127** was approached in two distinct ways. The first involved reaction of the former compound with ethyl diazoacetate in the presence of a metal catalyst $\{[(OAc)_2Rh]_2\}$ so as to effect cyclopropanation of the double-bond within compound **128**. This method had the attraction that it should allow for the direct production of a cyclopropane carboxylic acid derivative. In the event, however, slow addition of ethyl diazoacetate to a dichloromethane solution of olefin **128** containing rhodium(II) acetate dimer[139] gave at best, a 10% yield of the cyclopropyl-ester **134** which was obtained as a *ca.* 1:1 mixture of epimers (**Scheme 4.3**). Large quantities of diethyl fumarate (**135**) and diethyl maleate (**136**) were recovered from the reaction mixture and these products presumably arise through dimerization of the intermediate carbenoid.[139]



128 **134** **135** **136**

Scheme 4.3: *Reagents and Conditions*: (i) ethyl diazoacetate (6.0 mole equiv.), Rh_2OAc_4 (0.05 mole equiv.), CH_2Cl_2, reflux, slow addition, 12 h.

In principle, the difficulties mentioned above could be overcome by cyclopropanation of the olefin present within compound **128** using dibromocarbene since the resultant adduct would possess functionality that might allow for its elaboration, through the agency of metal-for-halogen exchange reactions, to compound **127**. To these ends, acetonide **128** was reacted with bromoform and aqueous sodium hydroxide in the presence of the phase-transfer catalyst triethylbenzylammonium chloride and in this manner a single dibromocarbene adduct, **137**, was obtained in 72% yield (**Scheme 4.4**). In keeping with related conversions,[73] it was assumed, at this point, that carbene addition had occurred at the less-hindered β-face of the double bond present within compound **128**. Subsequent X-ray crystallographic and chemical correlation studies (*vide infra*) proved that this assumption was correct.



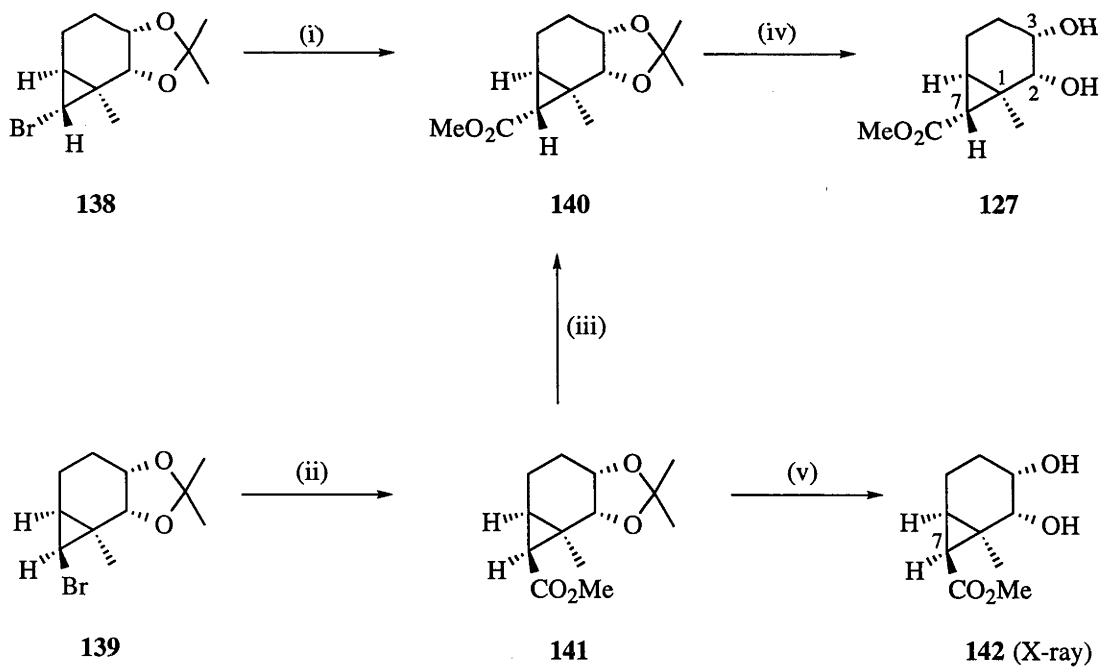
128 **137** **138** **139**

Scheme 4.4: *Reagents and Conditions*: (i) $CHBr_3$ (25.0 mole equiv.), 50% w/v aq. NaOH, TEBAC, C_6H_6, 5 °C to 20 °C, 16 h, 72%. (ii) Bu_3SnH (1.0 mole equiv.), C_6H_6, 5-20 °C, 16 h, 88%.

Dibromocarbene adduct **137** was subjected to reaction, at 0 °C, with one molar equivalent of tributyltin hydride and this resulted in formation of a *ca.* 2:1 mixture of the epimeric mono-bromo compounds **138** and **139** (88%). These products of reductive debromination, which could be separated from one another by flash column

chromatography, were easily differentiated by ^{1}H NMR spectroscopy. Thus, that epimer in which the vicinally related cyclopropyl protons are in a *trans*-relationship to one another (*viz.* compound **138**) displays a smaller coupling constant (J_{trans} = 4.0 Hz) than its counterpart in which there is a *cis*-relationship between the analogous protons (J_{cis} = 7.7 Hz).[140] Indeed, throughout the series of mono-substituted cyclopropanes prepared in connection with the synthesis of PSDP analogues the expectation that J_{cis} was always greater than J_{trans} was used to assign the stereochemistry of the non-hydrogen substituent at the apex of the three-membered ring (see **Table 4.1**). These structural assignments were confirmed by a single crystal X-ray analysis of a derivative of compound **139**.

Compound **138** was treated, at -96 °C, with a solution of *tert*-butylithium in hexane and the cyclopropyllithium species resulting from the ensuing metal-for-halogen exchange reaction was trapped with methyl chloroformate to give the corresponding cyclopropyl ester **140** (80%, **Scheme 4.5**). An analogous reaction involving compound **139** provided ester **141** in 83% yield. That these conversions proceeded



Scheme 4.5: *Reagents and Conditions*: (i) *t*-BuLi (2.0 mole equiv.), 0.2 h then methyl chloroformate (1.1 mole equiv.), Et_2O, -96°C, 2 h, 80%. (ii) *t*-BuLi (2.0 mole equiv.), 0.2 h then methyl chloroformate (1.1 mole equiv.), Et_2O, -96°C, 2 h, 83%. (iii) NaOMe (2.0 mole equiv.), MeOH, reflux, 16 h, 78%. (iv) AcOH (60% aq.), 80 °C, 16 h, 79%. (v) AcOH (60% aq.), 80 °C, 16 h, 72%.

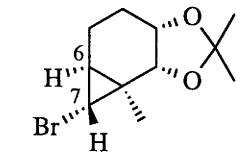
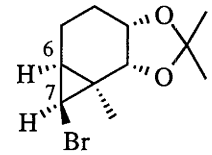
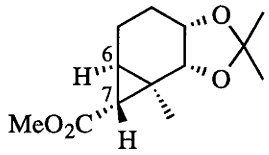
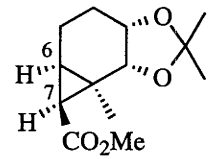
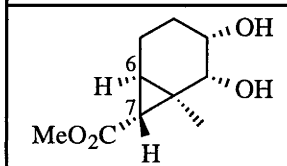
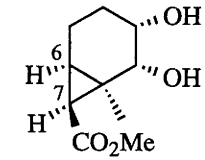
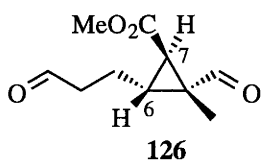
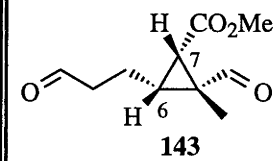
Compound	H7 (ppm)	$J_{6,7}$	Compound	H7 (ppm)	$J_{6,7}$
 **138**	2.84 ppm	$J_{6,7}$ = 4.0 Hz	 **139**	3.04 ppm	$J_{6,7}$ = 7.7 Hz
 **140**	1.50 ppm	$J_{6,7}$ = 5.2 Hz	 **141**	1.51-1.42 ppm	Could not be determined
 **127**	1.31 ppm	$J_{6,7}$ = 4.6 Hz	 **142**	1.46 ppm	$J_{6,7}$ = 9.0 Hz
 **126**	2.13 ppm	$J_{6,7}$ = 6.0 Hz	 **143**	2.13 ppm	$J_{6,7}$ = 8.9 Hz

Table 4.1: *$J_{6,7}$ Coupling Constants Observed in the ^1H NMR Spectra of Compounds* **126**, **127** *and* **138-143**.*,#

* All spectra recorded at 300 MHz in $CHCl_3$

The numbering systems used for the illustrated structures are not necessarily consistent with the Chemical Abstracts names but are used here to facilitate comparisons between structures.

with retention of stereochemistry was confirmed by ^{1}H NMR spectroscopic analyses (**Table 4.1**) and single crystal X-ray analyses of a species obtained later in the reaction sequences. Inspection of molecular models suggested that because of the *exo*-orientation of the ester moiety within compound **140** it should be less sterically congested than epimer **141**. On this basis, it seemed reasonable that under suitable reaction conditions, compound **141** could be epimerized to give the desired and more stable *exo*-isomer **140**. Indeed, when compound **141** was treated with sodium methoxide in refluxing methanol epimer **140** was obtained in 78% yield and as the exclusive product of reaction.

Hydrolysis of the isopropylidene unit within compound **141** was achieved using 60% aqueous acetic acid and gave compound **142** (79%, **Scheme 4.5**, **Table 4.1**) which was subjected to single-crystal X-ray analysis. This analysis (see **Figure 4.6**) established the *cis*-relationship between the vicinally-related cyclopropyl protons within this compound and, therefore, the *endo*-orientation of the carbomethoxy group at C7. Thus, these data, along with the ^{1}H NMR spectroscopic arguments advanced earlier, serve to establish the stereochemical relationship of the vicinally-related cyclopropyl protons within all of compounds **127** and **138**-**142**.

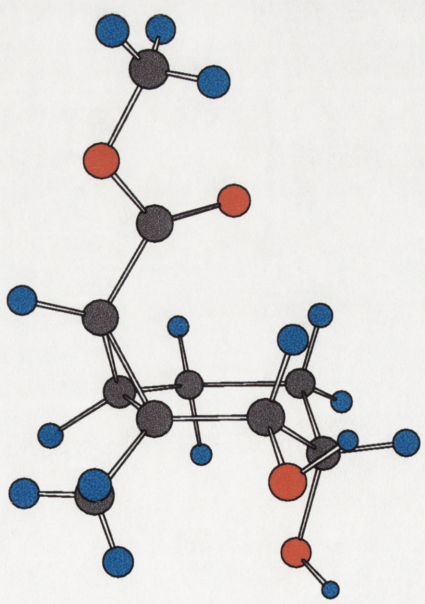
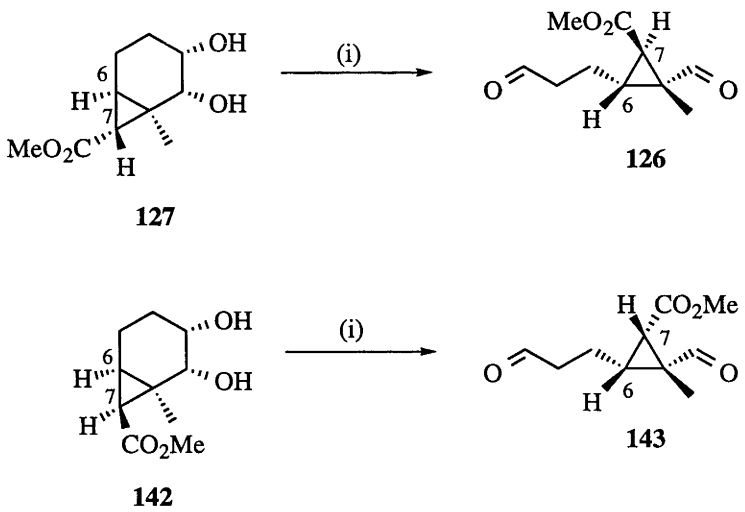


Figure 4.6: *CS Chem3D Pro™ Drawing of Compound* **142** *Generated Using Data Derived From an X-ray Crystallographic Study.*

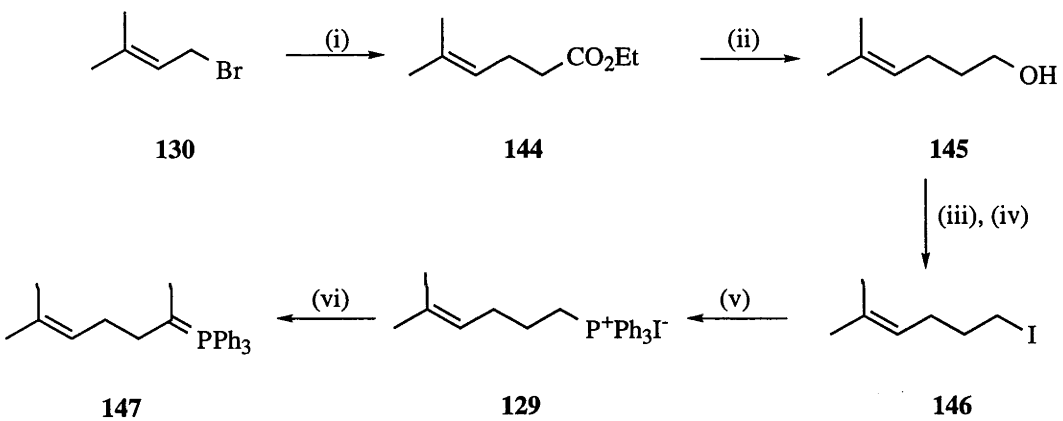
With significant quantities of compound **140** in hand studies towards the synthesis of the target molecule **111** were continued and involved initial removal of the acetonide group using 60% aqueous acetic acid. In this manner, diol **127** was obtained in 72% yield. Lead-tetraacetate-promoted cleavage of the diol moiety present within compound **127** afforded the corresponding acyclic dialdehyde **126** in high (91%) yield (**Scheme 4.6**). Isomer **143** was prepared in a similar fashion from precursor **142**. In the 300 MHz ^{1}H NMR spectrum of dialdehyde **126** the signal due to the hydrogen of the "neopentyl" aldehyde appears as a singlet at δ 9.37 while the one-proton doublet (J = 2.4 Hz) at δ 9.74 is assigned to the proton of the remaining aldehyde. The magnitude of the coupling ($J_{6,7}$= 6.0 Hz) between the vicinally-related cyclopropyl protons in compound **126** was smaller than that ($J_{6,7}$= 8.9 Hz) associated with epimer **143**.



Scheme 4.6: *Reagents and Conditions*: (i) $Pb(OAc)_4$ (3.0 mole equiv.), $CaCO_3$ (12.2 mole equiv.), CH_2Cl_2, 0 °C, 0.75 h, 91% for **126**; 95% for **143**.

A pivotal feature of the projected synthesis of compound **111** (**Figure 4.5**) was the expectation that regioselective Wittig olefination of dialdehyde **126** could be effected with ylide **147** derived from phosphonium salt **129**. Certainly, inspection of molecular models revealed that the "neopentyl" aldehyde present within compound **126** is more sterically encumbered than it's "normal" counterpart. Thus, under the correct set of reaction conditions preferential Wittig reaction of the latter aldehyde group might be expected.

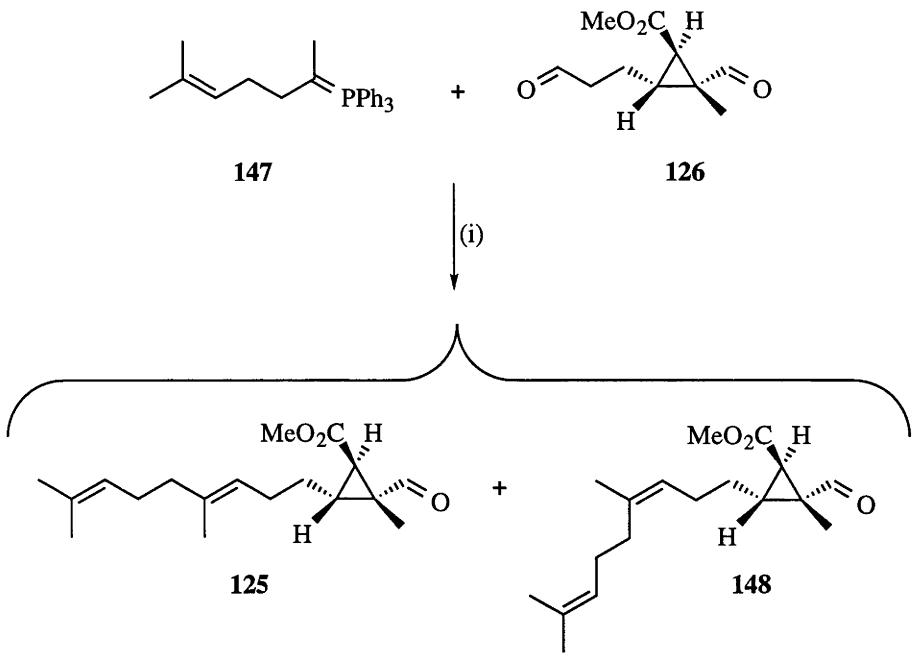
The required phosphonium salt, **129**, was synthesized according to known protocols (**Scheme 4.7**).[136] Thus, alkylation of the copper-lithium enolate anion of ethyl acetate[141] with 1-bromo-3-methyl-2-butene (**130**) provided the γ,δ-unsaturated ester **144** (97%) which was immediately converted to the corresponding alcohol, **145** (88%), *via* reduction with lithium aluminium hydride. This latter compound was subjected to reaction, at 0 °C, with methanesulfonyl chloride to furnish the corresponding mesylate, which was immediately displaced with sodium iodide in acetone to give iodide **146** (62% from **145**). Finally, iodide **146** and triphenylphosphine were stirred together in the dark at room temperature for 7 days. Filtration of the resultant powder afforded phosphonium salt **129** (45%) and the spectral data for this compound were in full accord with those reported previously.[136]



Scheme 4.7: *Reagents and Conditions*: (i) LDA (2.0 mole equiv.), EtOAc (2.0 mole equiv.), CuI (4.0 mole equiv.), THF, -110 °C, 1 h, 97%. (ii) $LiAlH_4$ (1.1 mole equiv.), Et_2O, 0 °C, 6 h, 88%. (iii) methanesulfonyl chloride (1.1 mole equiv.), NEt_3 (1.5 mole equiv.), CH_2Cl_2, 0 °C, 0.25 h. (iv) NaI (1.5 mole equiv.), acetone, 20 °C, 16 h, 62% from **145**. (v) PPh_3 (1.3 mole equiv.), C_6H_6, 20 °C, 7 days, 45%. (vi) *n*-BuLi (1.0 mole equiv.), THF, 0 °C, 0.25 h then MeI (1.0 mole equiv.), 0.25 h then *n*-BuLi (1.0 mole equiv.), 0.25 h.

Phosphonium ylide **147** was generated *in situ* by treatment of phosphonium salt **129** with a solution of *n*-butyllithium in hexane at 0 °C. Alkylation of this ylide with iodomethane and treatment of the resulting salt with a second aliquot of *n*-butyllithium then afforded the blood-red ylide **147**, which was cooled to -78 °C. Addition of this ylide, *via* cannula, to a cooled (-78 °C) solution of dialdehyde **126** in THF afforded,

after flash column chromatography, a *ca.* 2:1 mixture of compounds **125** and **148** (83% combined yield, **Scheme 4.8**).



Scheme 4.8: *Reagents and Conditions*: (i) inverse addition (*via* cannula), -78 °C, 1 h, 83%.

The geometry about the newly created carbon-carbon double-bond within these compounds can be assigned with confidence by inspecting the relative chemical shifts of the ^{13}C NMR resonances due to the methyl groups attached to this same double-bond. Thus, on the basis of literature precedence,[142-145] the more downfield resonance (δ 23.6) is attributed to that compound (**148**) possessing *Z*-geometry while the one at δ 16.2 is assigned to the target *E*-isomer **125**. Inspection of the 300 MHz ^{1}H NMR spectrum of the mixture of compounds **125** and **148** (**Figure 4.7**) reveals that all resonances due to analogous protons within these compounds are essentially coincident with the exception of the "neopentyl" aldehyde hydrogens which appear as singlets at δ 9.26 and 9.25 and in a *ca.* 2:1 ratio. The singlet nature of the aldehyde resonances in this spectrum indicates that the expected regioselectivity has been achieved in the Wittig reaction. The four-proton multiplet at δ 5.08 corresponds to the olefinic hydrogens present within compounds **125** and **148**. The six-proton singlet at δ 3.70 is ascribed to the ester methyl group protons within the two isomers. In the aliphatic region of the

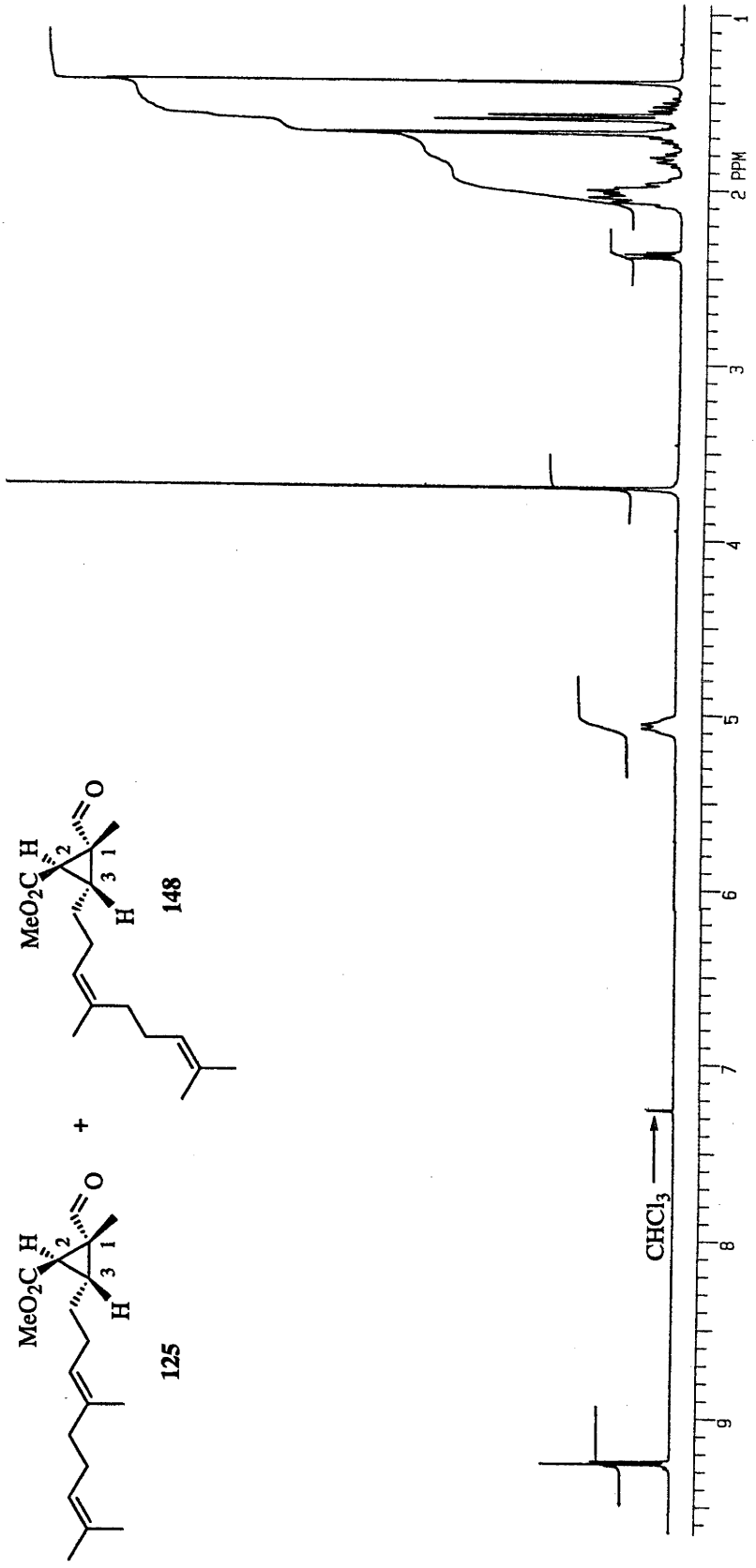


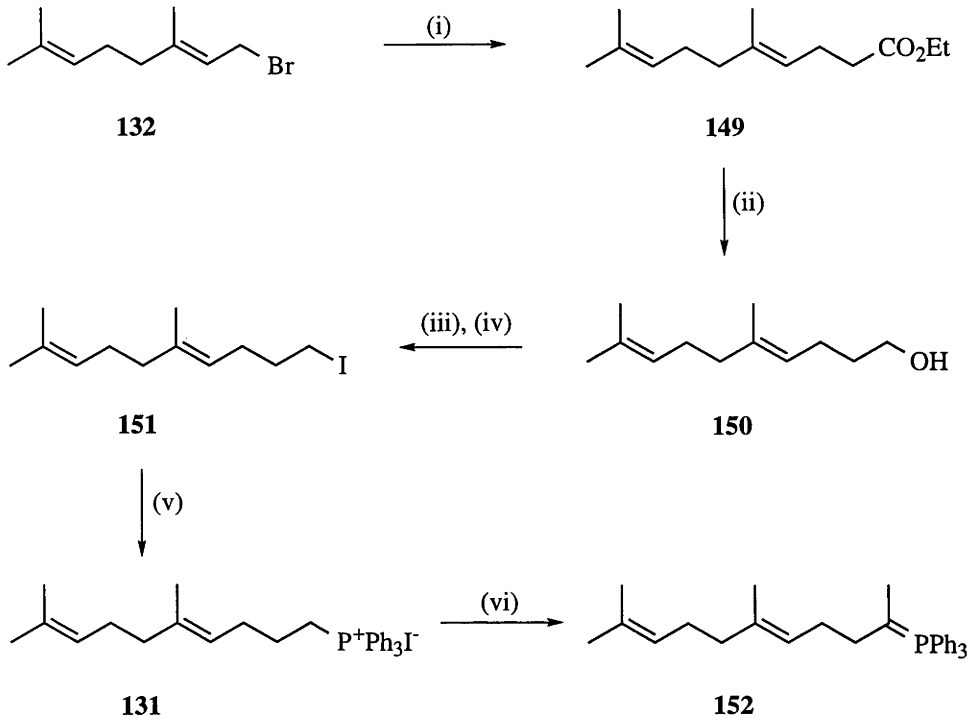
Figure 4.7: *300 MHz ^1H NMR Spectrum of a* ca. *2:1 Mixture of Compounds* **125** *and* **148**.

(Spectrum Recorded in $CDCl_3$ Solution)

spectrum the doublet at δ 2.33 (J = 6.5 Hz) is assigned to the hydrogen adjacent to the cyclopropyl ester. The complex multiplet at δ 2.04 is assigned to the eight methylene hydrogens present within the isoprenoid side-chain. The multiplet at δ 1.97 is attributed to the remaining cyclopropyl hydrogen, while three distinct olefinic-methyl resonances are apparent in the upfield region at δ 1.67, 1.60 and 1.58. A fourth and higher field methyl group resonance, at δ 1.39, is assigned to the cyclopropyl-methyl hydrogens within structures **125** and **148**.

Compounds **125** and **148** could not be separated from one another by flash chromatographic or HPLC techniques.[#] Furthermore, efforts to effect $Z \rightarrow E$ isomerization of the newly-formed double-bond within compound **148** by heating compounds **125** and **148** in the presence of thiophenol[146,147] did not significantly alter the ratio of isomers within the mixture. The consequent inability to separate compounds **125** and **148** meant that this mixture was carried into the next step of the reaction sequence in the hope that subsequent mixtures of products might prove separable. To these ends, phosphonium salt **131** was synthesized from geranyl bromide **132** in five steps and 30% overall yield (**Scheme 4.9**) by a procedure essentially identical with that previously described for the synthesis of congener **129**.[135] Thus, alkylation of the copper-lithium enolate anion of ethyl acetate with geranyl bromide **132** provided the ester **149** (100%), which was reduced with lithium aluminium hydride to the corresponding alcohol **150** (100%). Reaction of the derived mesylate with sodium iodide in acetone then gave iodide **151** (48% from **150**). Finally, reaction of compound **151** with triphenylphosphine gave the required phosphonium salt **131** (63%). The spectral data obtained on the latter compound were in full accord with those reported previously.[135]

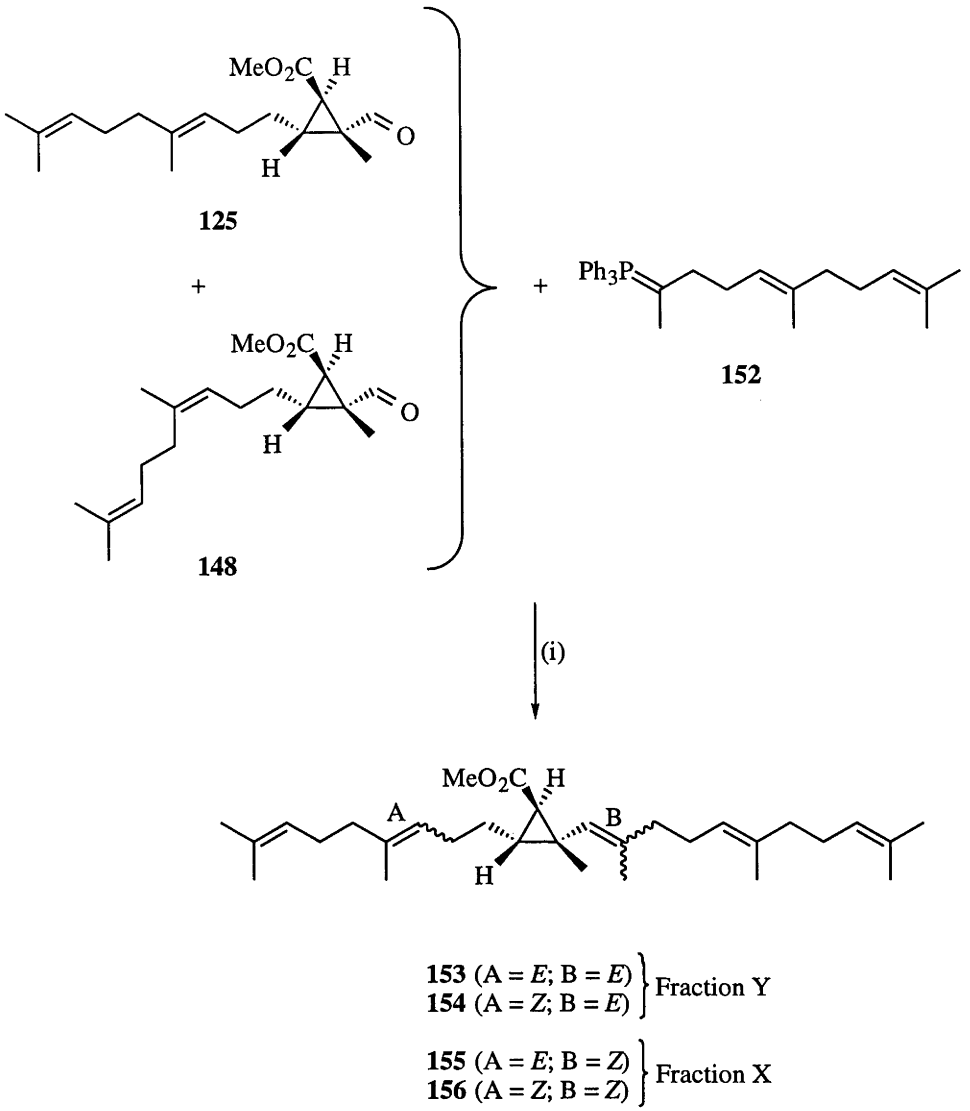
[#] The Horner[148] and Julia[149] olefin syntheses have also been utilized for the synthesis of tri-substituted alkenes. These methods have been reported to give favourable *trans*-selectivity which can be further tuned by judicious choice of base and solvent. However, in the present study, any amount of (Z)-isomer formed at this stage in the reaction sequence would be inseparable by HPLC techniques, and efforts to increase (*E*)/(Z)-selectivity in the olefination reaction were not pursued.



Scheme 4.9: *Reagents and Conditions*: (i) LDA (2.0 mole equiv.), EtOAc (2.0 mole equiv.), CuI (4.0 mole equiv.), THF, -110 °C, 1.5 h, 100%. (ii) $LiAlH_4$ (1.1 mole equiv.), Et_2O, 0 °C, 6 h, 100%. (iii) methanesulfonyl chloride (1.1 mole equiv.), NEt_3 (1.5 mole equiv.), CH_2Cl_2, 0 °C, 0.25 h. (iv) NaI (1.5 mole equiv.), acetone, 20 °C, 16 h, 48% from **150**. (v) PPh_3 (1.3 mole equiv.), C_6H_6, 20 °C, 7 days, 63%. (vi) *n*-BuLi (2.0 mole equiv.), THF, 0 °C, 0.25 h then MeI (2.0 mole equiv.), 0.25 h then *n*-BuLi (2.0 mole equiv.), 0.25 h.

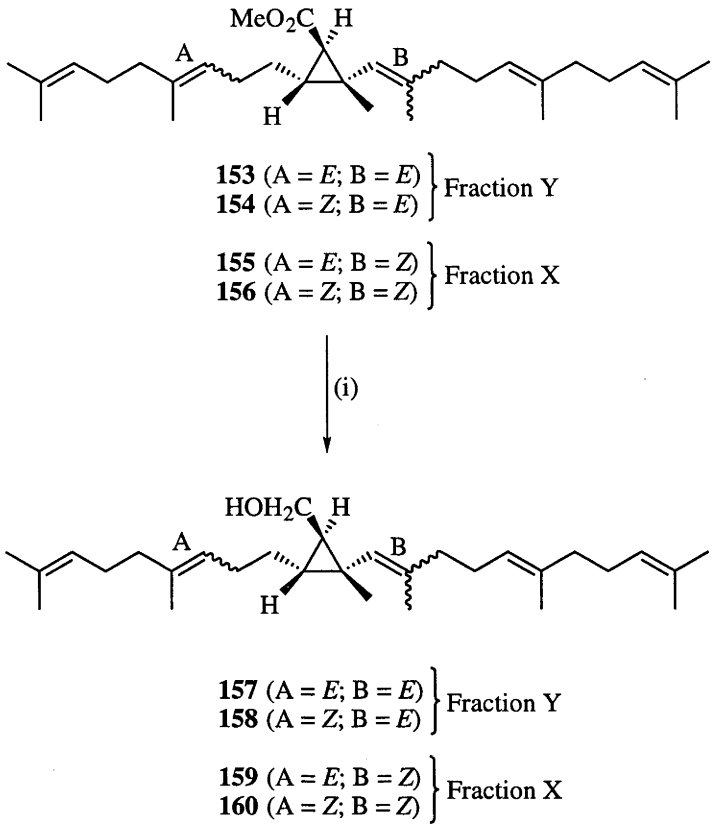
The ylide **152** was generated by initial reaction of salt **131** with *n*-butyllithium and treating the ylide so-formed with methyl iodide. The new phosphonium salt produced in this manner was then treated with a second aliquot of *n*-butyllithium to produce target **152**. This latter species was then reacted, *in situ*, with 0.5 molar equivalents of the *ca.* 2:1 mixture of compounds **125** and **148**. In this manner, a *ca.* 4:3:3:2 mixture (as judged by ^{13}C NMR analysis of the crude reaction mixture) of compounds **153-156** was obtained in 73% combined yield after flash chromatography (**Scheme 4.10**). Subjection of this mixture to semi-preparative HPLC on silica provided separation to the extent that two fractions [Fractions X (more mobile) and Y (less mobile)], were obtained and each of these contained two of compounds **153-156**.[+]

[+] The spectroscopic and structural assignments of compounds **153-156** and related compounds are discussed in more detail in a subsequent section (**4.9**).



Scheme 4.10: *Reagents and Conditions*: (i) inverse addition (*via* cannula), 0 °C, 16 h, 73%.

On the basis that derivatives of compounds **153-156** might be capable of further separation, fractions X and Y were each subjected to the next step in the reaction sequence. Thus, reduction of the ester moieties within the compounds associated with each of these fractions using lithium aluminium hydride gave the corresponding alcohols **157-160** (**Scheme 4.11**). However, the product alcohols contained within these fractions also proved to be inseparable by flash chromatographic and HPLC techniques.

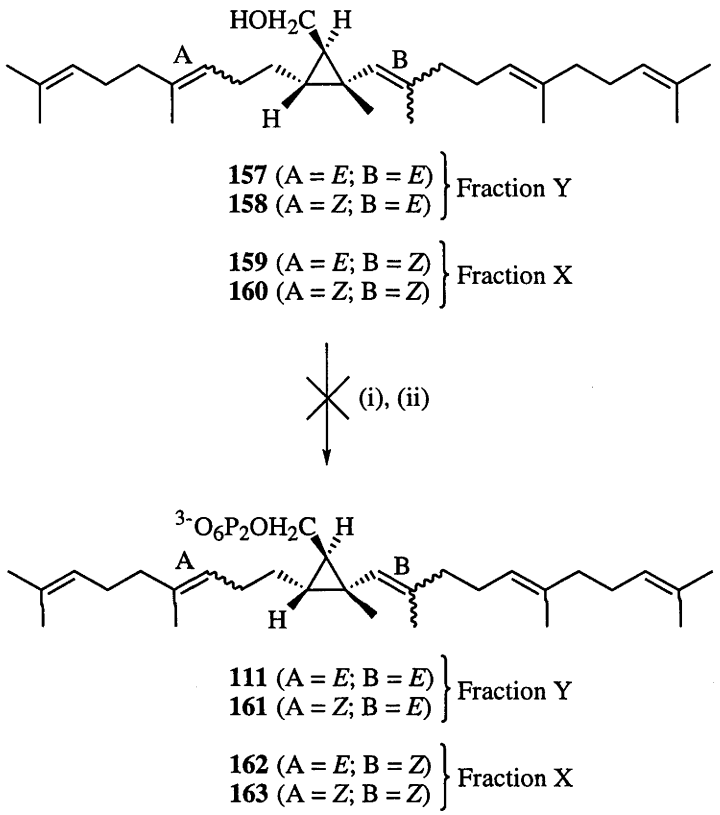


Scheme 4.11: *Reagents and Conditions*: (i) $LiAlH_4$ (3.5 mole equiv.), Et_2O, 0 °C, 3 h; 93% yield for Fraction X, 91% yield for Fraction Y.

4.7 Attempted Phosphorylation of Structural Analogues of Presqualene Alcohol

In an attempt to produce PSDP analogues that might be capable of inhibiting SQS, efforts were made to convert the primary alcohols **157-160** (obtained as mixtures in the manner described above) into their corresponding diphosphates using a protocol recently reported by Poulter *et al.* (**Scheme 4.12**).[135] Thus, the pairs of alcohols **157/158** and **159/160** derived from fractions X and Y, respectively, were each treated in with 1.2 equivalents of tetra-*n*-butylammonium diphosphate in the presence of an excess of trichloroacetonitrile to afford a *ca.* 2:1 mixture of monophosphorylated and diphosphosphorylated products, together with recovered starting material (*ca.* 10%). After purification on a hydrophobic Sephadex LH-20 column, the two monophosphate fractions, each containing a pair of compounds, were independently reacted with diphenylchlorophosphate and the very modest amounts of tetrabutylammonium

diphosphate thus obtained were subjected to Sephadex LH-20 chromatography. For comparative biological studies it was considered necessary to replace the tetra-*n*-butylammonium cation with an ammonium ion. To these ends, the diphosphate mixtures were passed through a cation-exchange chromatography column but subjection of the eluted fractions to preparative-scale reversed-phase HPLC[150] failed to provide any of the anticipated PSDP analogues **111** and **161-163**.*



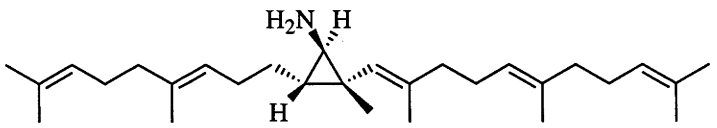
Scheme 4.12: *Reagents and Conditions*: (i) (*n*-$Bu_4N)H_2PO_4$ (1.2 mole equiv.), CCl_3CN, CH_3CN, 20 °C, 1 h. (ii) $(PhO)_2POCl$ (1.0 mole equiv.), Bu_3N (2.0 mole equiv.), (*n*-$Bu_4N)H_2PO_4$ (3.4 mole equiv.), C_6H_5N, 5 h.

4.8 Synthesis of Ammonium Analogues of Presqualene Diphosphate

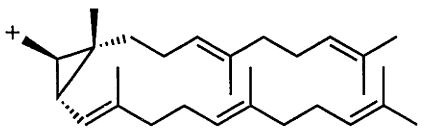
The difficulties noted above regarding the acquisition of PSDP analogue **111** and its various geometrical isomers prompted consideration of methods for preparing the primary amine **164**, the ammonium salt of which could be considered as an analogue

* Similar problems associated with cation exchange reactions involving other PSDP analogues have been noted by R. Coates and his colleagues working at the University of Illinois, Urbana-Champaign (personal communication from R. Coates to M. Banwell, 4/11/98).

of the first formed carbocationic intermediate, **115**, associated with the conversion of PSDP into squalene (see **Figure 4.3**, page 56). Acquiring compound **164** seemed a worthwhile objective since related amines, e.g. **119**, have proven to be good inhibitors of SQS. To these ends, the esters **153-156** contained within fractions X and Y were

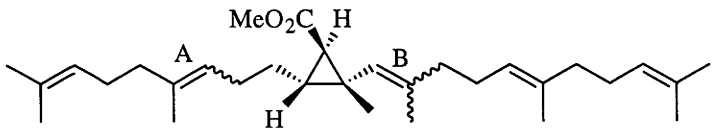


164



115

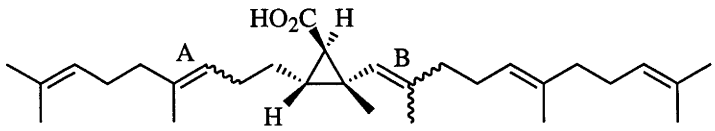
hydrolyzed to the corresponding pairs of carboxylic acids **165-168** (**Scheme 4.13**). Following protocols developed by Poulter *et al.*,[127] introduction of the required amine moiety was achieved using Curtius rearrangement procedures. Thus, the pairs of compounds **165/166** and **167/168** were each heated at 100 °C for 30 minutes with diphenyl phosphorazidate, and the isocyanates thus formed were intercepted with 2-trimethylsilylethanol to provide, after standard aqueous work-up, the pairs of carbamates **169/170** and **171/172**. These carbamates were then cleaved with tetra-*n*-butylammonium fluoride so as to provide the amine pairs **164/173** and **174/175** targeted for biological assay. It was found that these amines were very susceptible to decomposition, even when stored at -20 °C under a nitrogen atmosphere. As a consequence, all efforts to isolate the individual components of these mixtures by HPLC techniques proved fruitless.



153 (A = *E*; B = *E*)
154 (A = *Z*; B = *E*) } Fraction Y

155 (A = *E*; B = *Z*)
156 (A = *Z*; B = *Z*) } Fraction X

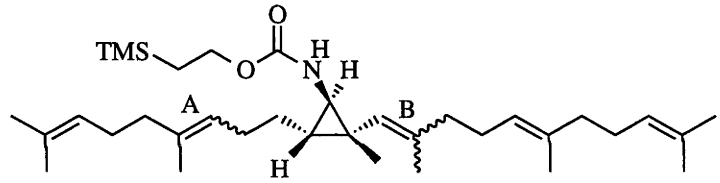
(i)



165 (A = *E*; B = *E*)
166 (A = *Z*; B = *E*) } Fraction Y

167 (A = *E*; B = *Z*)
168 (A = *Z*; B = *Z*) } Fraction X

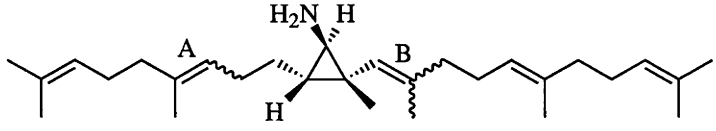
(ii)



169 (A = *E*; B = *E*)
170 (A = *Z*; B = *E*) } Fraction Y

171 (A = *E*; B = *Z*)
172 (A = *Z*; B = *Z*) } Fraction X

(iii)



164 (A = *E*; B = *E*)
173 (A = *Z*; B = *E*) } Fraction Y

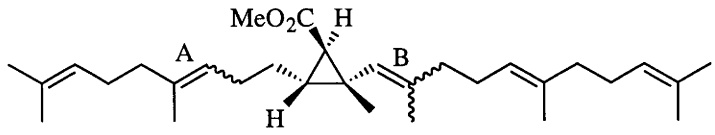
174 (A = *E*; B = *Z*)
175 (A = *Z*; B = *Z*) } Fraction X

Scheme 4.13: *Reagents and Conditions*: (i) KOH, MeOH, 20 °C, 16 h. (ii) $(PhO)_2PON_3$ (1.0 mole equiv.), 100 °C, 0.5 h then $TMS(CH_2)_2OH$ (1.0 mole equiv.), 50 °C, 12 h. 62% yield for Fraction X, 73% yield for Fraction Y. (iii) TBAF, 50 °C, 1 h. 35% yield for Fraction X, 60% yield for Fraction Y.

4.9 Spectroscopic Analysis of Presqualene Diphosphate Analogues

Considerable efforts were made to establish the full structures of the esters **153-156** contained within fractions X and Y as well as compounds derived from each of these fractions. Confident assignment of the structures of these compounds followed from analysis of the ^{13}C NMR chemical shifts of the signals due to the carbons of the methyl groups at the two double-bonds (A and B) established through Wittig chemistry as well as analysis of the chemical shifts of the cyclopropyl methyl carbons. The first part of the argument associated with these assignments centres on the chemical shift of the signals due to the latter carbons. The relevant signals in each fraction were assigned on the basis of the initial assumption that the signals due to the protons of this group will resonate at higher field in the ^{1}H NMR than those due to their counterparts in any of the other methyl groups within these compounds. Using HETCOR techniques the signals due to the cyclopropyl methyl carbons could then be identified and in the ^{13}C NMR spectrum of fraction X these appeared as overlapping signals at δ 20.5 while in fraction Y these were also observed as overlapping signals, but now at δ 19.7 (**Tables 4.2** and **4.3**). Clearly then, there was some reasonable variation in the chemical shift of this carbon atom. Given that there is only one such signal in the ^{13}C NMR spectrum of each fraction and that the structural feature most likely to affect the chemical shift of this carbon is the geometry about the nearby double-bond (B) in the farnesyl side-chain, then it is proposed that the two compounds in each fraction have the same geometry (*E* or *Z*) about this (B) double bond.

The second key assumption is based on the well-substantiated[142-145,151,152] argument that the carbons of methyl groups associated with *Z*-configured double-bonds resonate in the range *ca.* δ 20.5-24.0 while their counterparts in *E*-configured alkenes appear at significantly higher field, *viz. ca.* δ 16.0-17.0. Some relevant comparisons are shown in **Figure 4.8**.[143,135]



153 (A = *E*; B = *E*)
154 (A = *Z*; B = *E*)
} Fraction Y

155 (A = *E*; B = *Z*)
156 (A = *Z*; B = *Z*)
} Fraction X

RESONANCE	CHEMICAL SHIFT	ASSIGNMENT
A	23.8 ppm	(*Z*)-CH_3
B	22.9 ppm	(*Z*)-CH_3
C	20.5 ppm	cyclopropyl-CH_3
D	18.0 ppm	(*E*)-CH_3
E	17.9 ppm	(*E*)-CH_3
F	16.3 ppm	(*E*)-CH_3

Table 4.2: *^{13}C NMR Chemical Shifts of Methyl Groups Within Compounds* **153** *and* **154** *in the region* δ *25.0-15.0* (**Fraction X**).

RESONANCE	CHEMICAL SHIFT	ASSIGNMENT
A	23.7 ppm	(*Z*)-CH_3
B	19.7 ppm	cyclopropyl-CH_3
C	18.0 ppm	(*E*)-CH_3
D	17.1 ppm	(*E*)-CH_3
E	16.4 ppm	(*E*)-CH_3
F	16.3 ppm	(*E*)-CH_3

Table 4.3: *^{13}C NMR Chemical Shifts of Methyl Groups Within Compounds* **155** *and* **156** *in the region* δ *25.0-15.0* (**Fraction Y**).

Inspection of the ^{13}C NMR spectra of Fractions X and Y reveals that in the spectrum of the latter there is only one signal, at δ 23.7, due to a methyl group associated with a *Z*-configured double-bond. By comparison, in the spectrum of fraction X two signals,

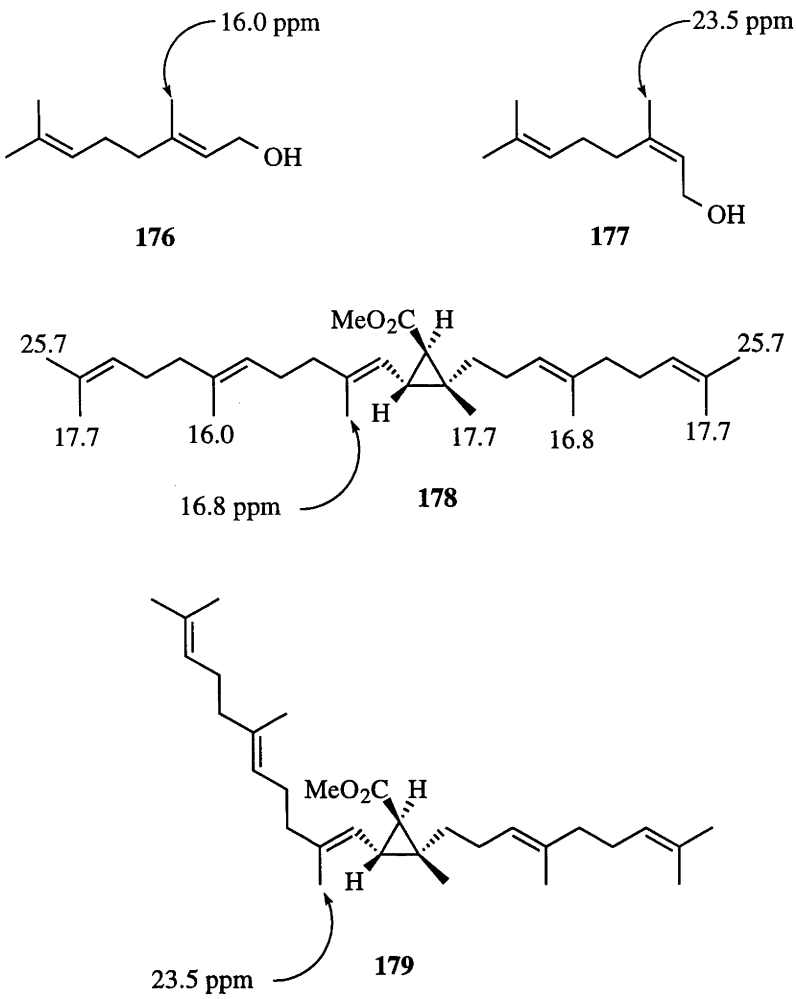


Figure 4.8: *Selected ^{13}C NMR Chemical Shifts for* (E)- *and* (Z)- *Terpenes.*

at δ 23.8 and 22.9, are observed in this region and given that the intensity of the lower field of these is twice the intensity of the other this is taken to imply these are methyl groups associated with three *Z*-configured double-bonds in this sample. Taken together, all these data strongly suggest that fraction Y contains compounds **153** and **154** while fraction X contains compounds **155** and **156**.

The spectroscopic "trends" presented above for esters **153-156** continue throughout the series of compounds derived there-from and, therefore, support structural assignments made throughout this series of PSDP analogues.

4.10 Biological Evaluation of Presqualene Diphosphate Analogues 164 and 173-175

Despite the susceptibility of amines **164** and **173-175** to decomposition, 3.6 milligrams of Fraction X were recovered and have been submitted for biological testing.[&] These compounds are being tested as inhibitors of the enzyme squalene synthase (SQS) in a standard assay with farnesyl diphosphate. To date, however, the results of such tests are not available.

4.11 Summary

An efficient and enantioselective first-generation synthesis of amine analogues, **164** and **173-175**, of presqualene diphosphate has been achieved using *cis*-1,2-dihydrocatechol **17**, derived by microbial oxidation of toluene, as starting material. The atom-economical sequences used serve to highlight the potential utility of microbially-derived *cis*-1,2-dihydrocatechols in the preparation of mono-chiral cyclopropanes.

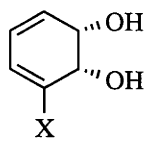
[&] These compounds have been submitted to Professor Dale Poulter (Department of Chemistry, University, Salt Lake City, Utah 84112) for biological evaluation.

CHAPTER FIVE

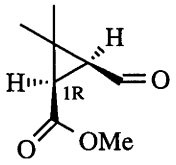
Synthesis of Polycyclopropanes Related to the Natural Products FR-900848 and U-106305

5.1 Introduction

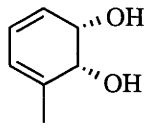
In the preceding two chapters means for converting *cis*-1,2-dihydrocatechols **14** (X=Br) and **17** into the biologically significant chiral (non-racemic) cyclopropanes **87** and **164/173-175**, respectively, were described.



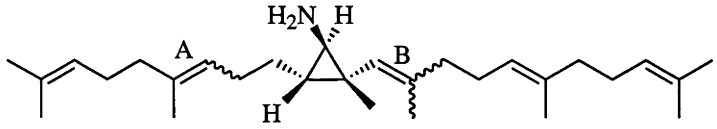
14 (X=Br)



87



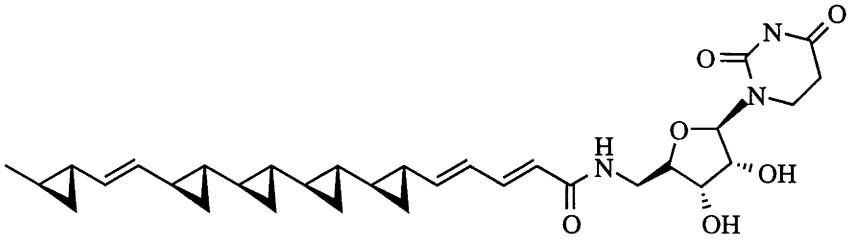
17



164 (A = *E*; B = *E*)
173 (A = *Z*; B = *E*) } Fraction Y

174 (A = *E*; B = *Z*)
175 (A = *Z*; B = *Z*) } Fraction X

The aim of the work described in this chapter was to examine the potential of *cis*-1,2-dihydrocatechols as starting materials for the construction of polycyclopropyl compounds related to the natural products FR-900848 (**180**) and U-106305 (**181**). However, prior to discussing such work, some background commentary on these structurally remarkable target molecules (**180** and **181**) is required.



180 (FR-900848)

181 (U-106305)

5.2 Biological Significance of the Polycyclopropane-Containing Natural Products FR-900848 and U-106305

There is considerable concern, especially amongst the medical profession, regarding fungal disease. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carnii* and *Aspergillis fumigatus* are the cause of high morbidity and mortality in patients who have AIDS, diabetes or immune systems suppressed by drugs.[153] Although rarely fatal, dermatophtye-type infections such as *Tinea pedis* and *Candidiasis* are widespread throughout the world. Current therapies for the treatment of serious fungal infections are deficient and, as such, several pharmaceutical companies world-wide are focussing their efforts to develop superior anti-infective agents.

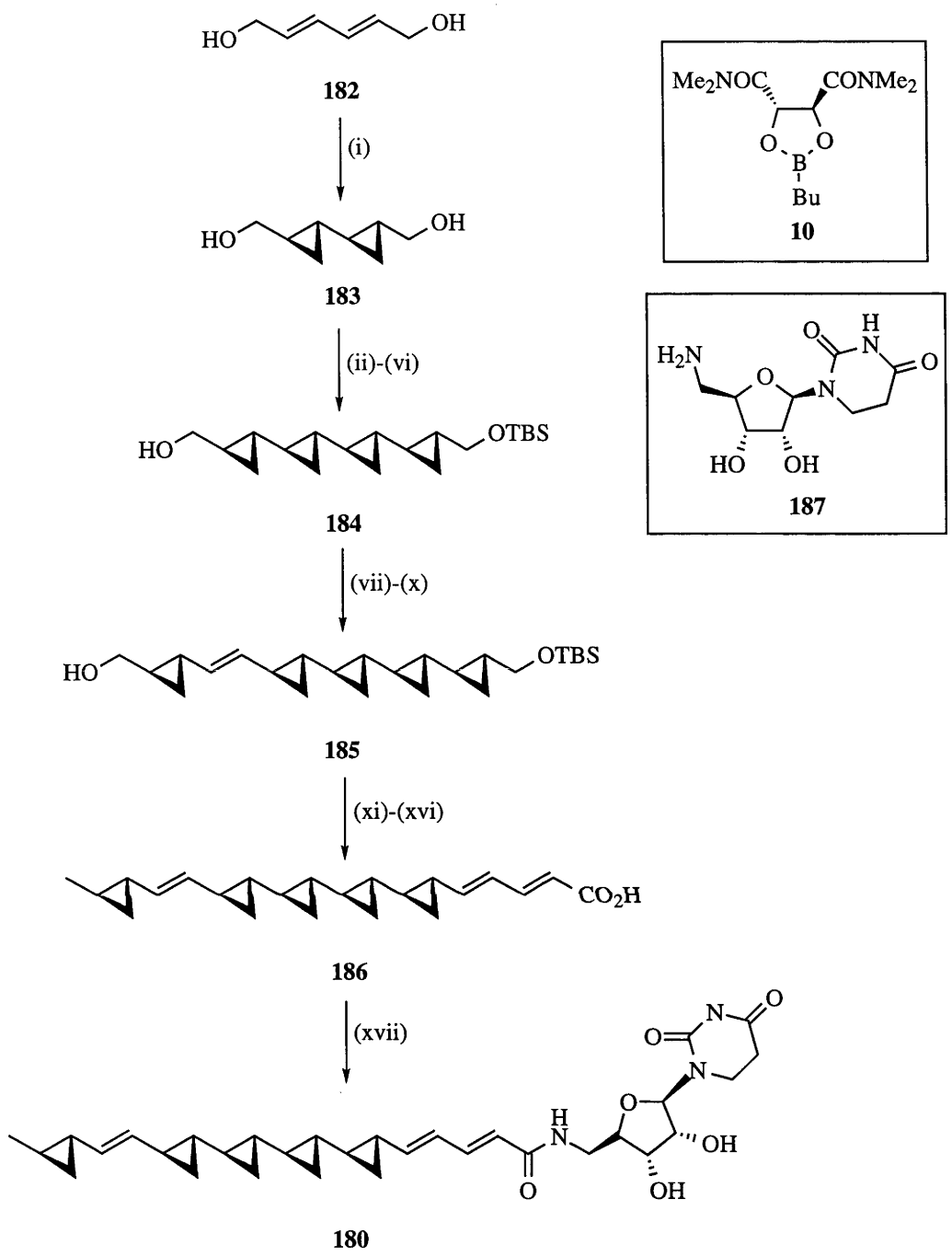
Fermentation broths are typically rich in novel anti-infective compounds, due to evolutionary pressures of microbial antagonism and the isolation and structural elucidation of such agents plays a significant role in the discovery of new therapeutic agents. In 1990 Yoshida *et al.* reported the isolation and partial structural elucidation of FR-900848 (**180**), an anti-fungal pentacyclopropane nucleoside natural product produced by *Streptoverticillum fervens*.[154] FR-900848 (**180**) shows useful activity against filamentous fungi such as *Aspergillus niger*, *Mucor rouxianus* and *Fusarium oxysporum*, with inhibiting concentrations as low as 0.05 micrograms per mL. In contrast, the compound is essentially inactive against non-filamentous fungi such as *Candida albicans* as well as Gram-positive and -negative bacteria.[153,155] Compound **180** displays low mammalian toxicity, with an LD_{50} of 1 g per kg of body weight in mice. The polycyclopropyl array associated with FR-900848 is structurally remarkable but the role that this conformationally restricted fatty-acid type side-chain plays in the bioactivity and mode of action of the compound remains unclear.

Recently, Upjohn scientists reported the isolation of U-106305 (**181**), a metabolite from the fermentation broth of *Streptomyces sp.* UC-11136.[156] U-106305, which inhibits the plasma protein cholesteryl ester transfer protein (CETP), shows a striking similarity to FR-900848 (**180**) and is structurally remarkable being graced with six cyclopropane rings, five of which are contiguously related.

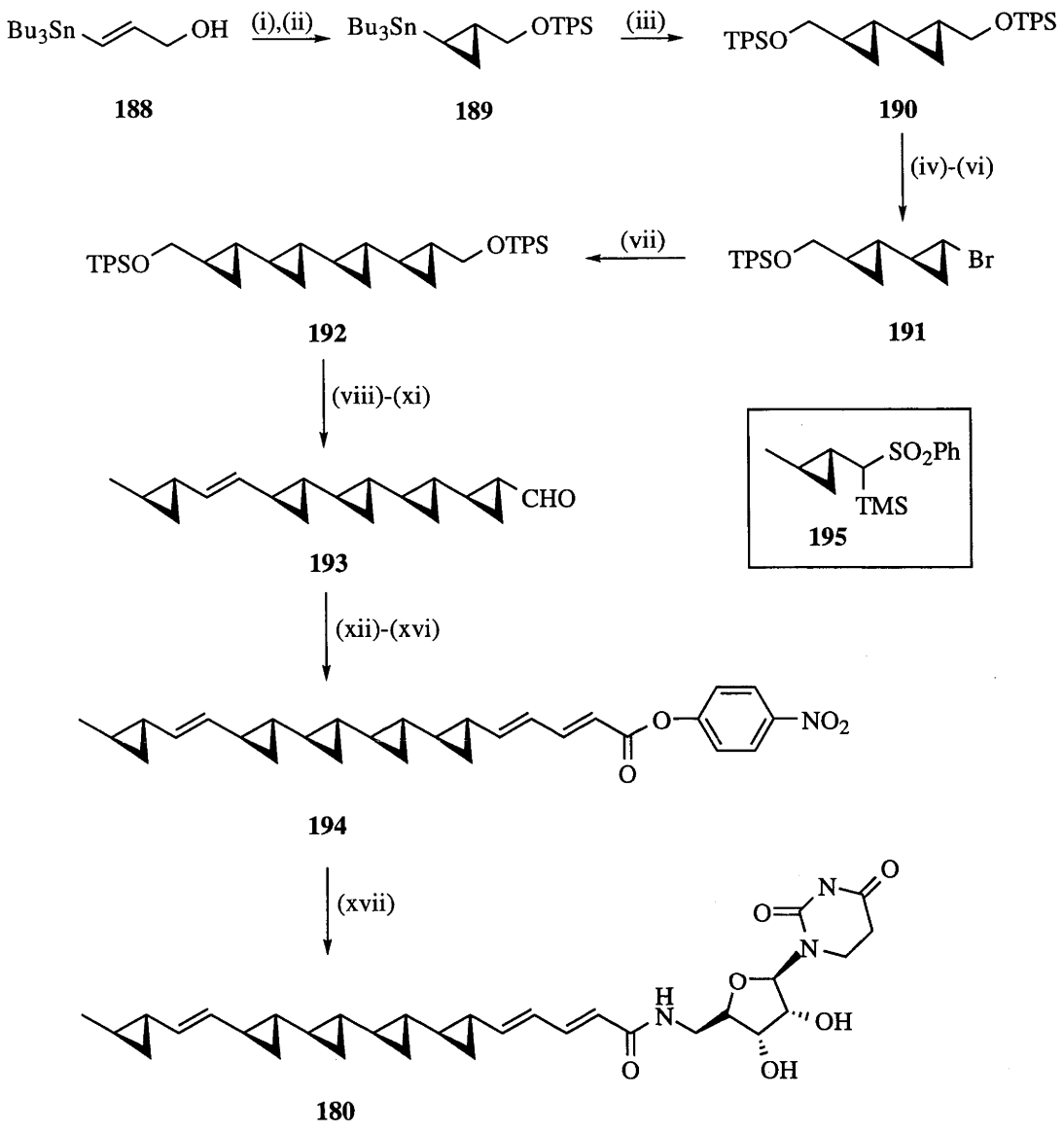
5.3 Established Methods for the Synthesis of FR-900848 and U-106305

Barrett *et al.* recently reported[157] a total synthesis of FR-900848 (**180**) and used Charette asymmetric cyclopropanation chemistry to control the stereocentres present within the side-chain of this compound (**Scheme 5.1**). Thus, mucandiol **182** was exhaustively cyclopropanated in the presence of the chiral auxiliary **10**[34] to provide bicyclopropane **183** in high enantiomeric excess. Pyridinium chlorochromate (PCC)-promoted oxidation of the latter compound and immediate subjection of the product dialdehyde to Wittig-Horner olefination provided the expected (*E,E*)-diester. DIBAL-H reduction of this diester and bicyclopropanation of the resulting *bis*-allylic alcohol, again using Charette methodology, then provided a quatercyclopropane, which after selective mono-protection gave compound **184** which was essentially uncontaminated with any other diastereomers. This intermediate was further elaborated to quinquecyclopropane **185** which was, in turn, converted into compound **186**. Finally, *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride mediated coupling of the latter compound with the nucleoside amine **187** gave FR-900848 (**180**).

Falck *et al.* have also reported a total synthesis of FR-900848 (**Scheme 5.2**).[158] Thus, Charette cyclopropanation[34] of vinylstannane **188** and silylation of the derived cyclopropylmethanol provided stannane **189** in 90% ee which was *trans*-metallated with *sec*-butyllithium. The anion thus formed was added to $[ICuPBu_3]_4$ and the resulting conjugate subjected to an oxygen induced[159,160] dimerization at low temperature so as to give bicyclopropane **190** in 98% ee. The observed enrichment in enantiomeric composition is a result of the statistical distribution of products and represents a variation of the Horeau amplification principle.[158] Using standard methods, compound **190** was converted into the corresponding carboxylic acid which was, in turn, subjected to a bromo-decarboxylation (Hünsdiecker) reaction[161] thereby giving compound **191**. A repetition of the dimerization protocol transformed this latter compound into quatercyclopropane **192**. Partial deprotection of compound **192** and



Scheme 5.1: *Reagents and Conditions*: (i) **10**, Et_2Zn, CH_2I_2, CH_2Cl_2, 0 °C to 20 °C, 89%. (ii) PCC, NaOAc, CH_2Cl_2, 0 °C to 20 °C. (iii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 67% from **183**. (iv) DIBAL-H, CH_2Cl_2, -78 °C, 94%. (v) **10**, Et_2Zn, CH_2I_2, DME, -15 °C to 20 °C, 93%. (vi) NaH, TBSCl, THF, 44%. (vii) PCC, NaOAc, CH_2Cl_2, 0 °C to 20 °C. (viii) (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 0 °C to 20 °C, 90%. (ix) DIBAL-H, CH_2Cl_2, -78 °C, 91%. (x) **10**, Et_2Zn, CH_2I_2, CH_2Cl_2, -40 °C, 90%. (xi) *N*-(phenylsulfenyl)succinimide, Bu_3P, C_6H_6, 89%. (xii) Raney Ni, EtOH, -40 °C. (xiii) NH_4F, EtOH, 65 °C. (xiv) PCC, NaOAc, CH_2Cl_2, 0 °C to 20 °C. (xv) (*E*)-$MeO_2CCH{=}CHCH_2P(O)(OMe)_2$, NaH, THF, 20 °C. (xvi) $KO(TMS)_3$, CH_2Cl_2, 85%. (xvii) **187**, *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride, Et_3N, 69%.



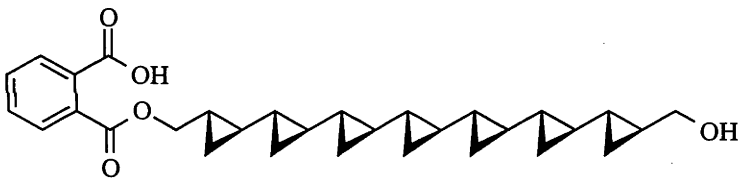
Scheme 5.2: *Reagents and Conditions*: (i) **10**, Et_2Zn, CH_2I_2, CH_2Cl_2, 20 °C, 98%. (ii) TPSCl, imidazole, DMF, 20 °C, 88%. (iii) *s*-BuLi, THF, -40 °C; $[ICuPBu]_4$, -78 °C; O_2, -78 °C, 73%. (iv) TBAF, THF, 20 °C, 72%. (v) $RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$ (1:1:1.5), 20 °C, 91%. (vi) 2-mercaptopyridine-*N*-oxide, DMAP, $BrCCl_3$, 20 °C, *hv*, 77%. (vii) *t*-BuLi, THF, -40 °C; $[ICuPBu]_4$, -78 °C; O_2, -78 °C, 75%. (viii) TBAF, THF, 20 °C, 72%. (ix) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2, 20 °C, 91%. (x) **195**, *n*-BuLi, THF, -78 °C, 65%. (xi) Li, naphthalene, THF, -78 °C, 70%. (xii) TBAF, THF, 20 °C, 95%. (xiii) TPAP, NMO, 4Å molecular sieves, CH_2Cl_2, 20 °C, 91%. (xiv) (*E*)-$EtO_2CCH{=}CHCH_2P(O)(OEt)_2$, $LiN(TMS)_2$, THF, -78 °C to 20 °C, 89%. (xv) LiOH, $MeOH/H_2O$. (xvi) DMAP, 4-nitrophenol, CH_2Cl_2, 20 °C, 73%. (xvii) **187**, DMF, 76%.

Ley-Griffith oxidation of the resulting alcohol then provided the corresponding aldehyde which readily reacted with the α-anion of sulfone **195**. Further manipulation of the product sulfone then gave the new aldehyde **193**. Horner-Emmons chain-extension of compound **193** followed by *trans*-esterification with 4-nitrophenol then

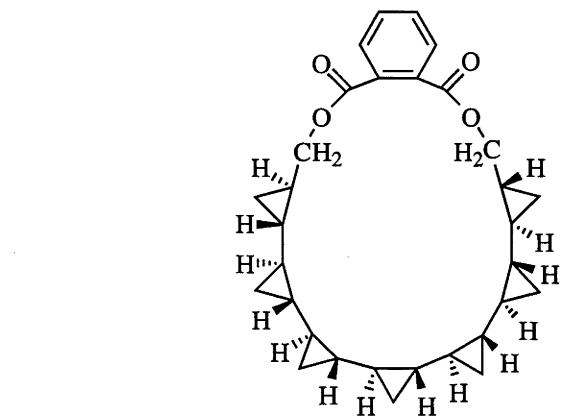
provided the ester **194**. Finally, reaction of 5'-deoxy-5,6-dihydrouridine (**187**) with compound **194** in DMF at room temperature gave FR-900848.

Two total syntheses of U-106305 (**181**) have also been reported recently, one by Barrett[162] and the other by Charette.[163] Both use a bidirectional strategy that is closely related to the syntheses discussed for FR-900848 (**180**).

FR-900848 and U-106305 also provide intriguing model compounds upon which to base a new class of materials - the stereoregular polycyclopropanes. Such compounds may well have unique and useful physical properties. Indeed, extensive crystallographic studies has shown that all-*syn-trans*-disubstituted cyclopropane oligomers containing three to seven cyclopropane rings are helical, at least in the solid state.[162,164] Recently, and in an effort to further pursue the materials science possibilities associated with polycyclopropyl arrays, *syn-trans*-1,21-septecyclopropane **196** was macrolactonized to give the corresponding coronane **197**, a dilactone comprising a 22-membered ring (**Scheme 5.3**).[165]



196



197

Scheme 5.3: *Reagents and Conditions*: (i) 2,4,6-$Cl_3C_6H_2COCl$, NEt_3, DMAP, reflux, THF, 74%.

The foregoing discussion serves to highlight the potential importance of polycyclopropyl arrays. As a consequence, new methods for their synthesis continue to be sought.[166] It was envisaged that *cis*-1,2-dihydrocatechols could be exploited as starting materials for the construction of this alluring class of compounds, and the methods for achieving this are discussed in the following section.

5.4 Chemoenzymatic Approaches to the Quatercyclopropyl Sub-Structures Associated with FR-900848 and U-106305

Initial efforts focussed on diester **198** as the synthetic target and the idea that stereoselective and exhaustive cyclopropanation of compound **201** would give the quatercyclopropane **200** which, after oxidative cleavage of the *cis*-diol moieties, would deliver the related *tetra*-aldehyde **199** (**Figure 5.1**). Two further aspects of the

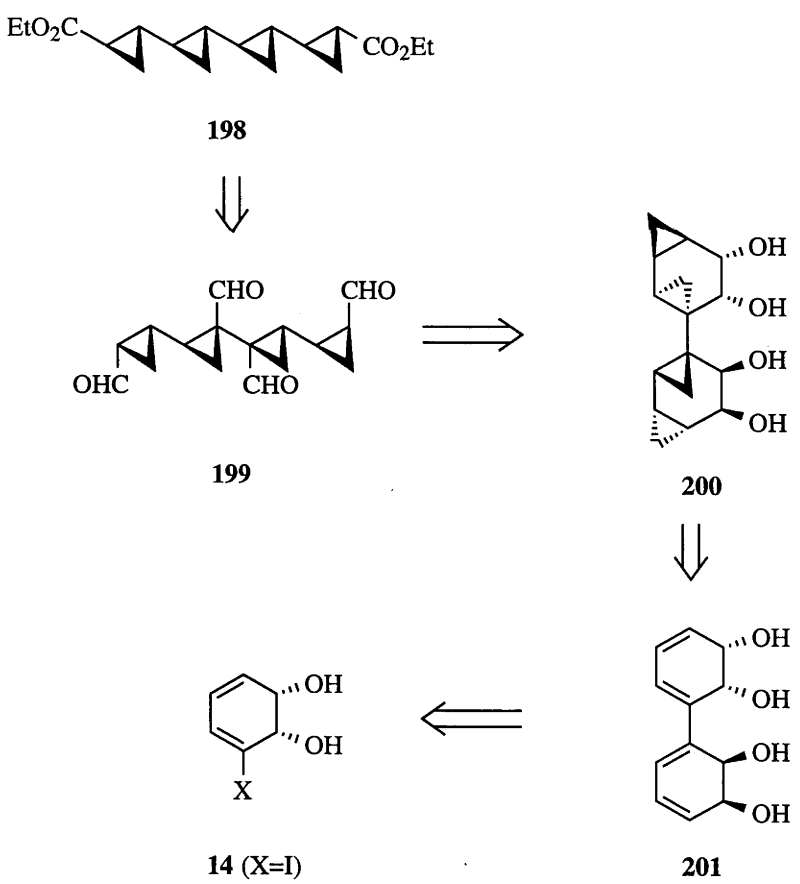


Figure 5.1: *Retrosynthetic Analysis of Compound **198** Based Upon Using the Iodobenzene-derived cis-1,2-Dihydrocatechol **14** (X=I) as Starting Material.*

approach were (i) that compound **201** might be accessible *via* Ullmann-type coupling of the enantiopure *cis*-1,2-dihydrocatechol **14** (X=I) derived by microbial oxidation of iodobenzene and, (ii), that the terminal aldehyde groups within compound **199** could, on steric grounds, be selectively oxidized to the corresponding carboxylic acid groups while, if desired, the internal aldehyde moieties could be deleted using Wilkinson's catalyst, a system known[167] to effect decarbonylation of tertiary cyclopropane carboxaldehydes with retention of configuration. In principle, the *cis*-relationship between the two cyclopropane ring substituents at either end of compound **199** could be changed into the thermodynamically more favoured *trans*-relationship *via* base-catalyzed epimerization* and thereby delivering compound **198**, an obvious precursor to the key intermediate **192** associated with Barrett's synthesis of FR-900848 (**180**). Of course, and perhaps more significantly, the chemistry implied by **Figure 5.1** should allow for the synthesis of a range of interesting analogues of FR-900848 (**180**) and U-106305 (**181**).

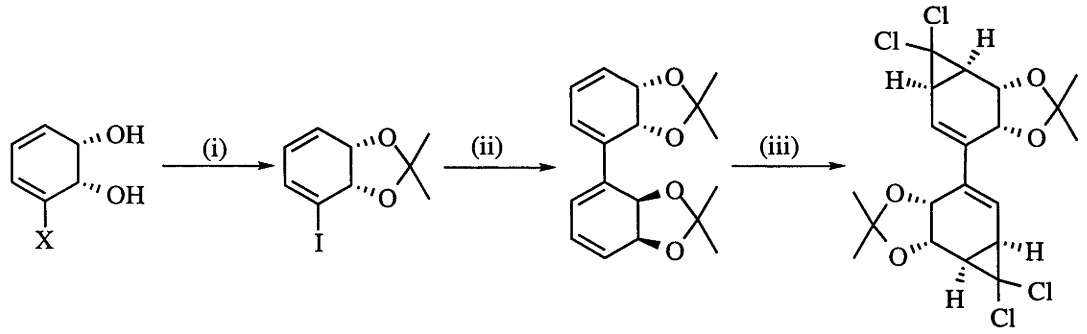
In initial attempts (**Scheme 5.4**) to implement the ideas outlined above, the acetonide derivative, **202**,[168] of diol **14** (X=I) was metallated with *tert*-butyllithium in pentane at -96 °C and the resulting lithio-species *trans*-metallated using zinc chloride. The organozinc species so-formed was then subjected to Negishi cross-coupling[169] with iodide **202** and the *tetra*-ene **203** (40%) was thereby obtained.# Not surprisingly, this hitherto unknown and interesting "dimer", which cannot be accessed *via* microbial oxidation of biphenyl, was found to be highly susceptible to dimerization and aromatization, especially when exposed to even mildly acidic reagents such as silica gel. To circumvent such difficulties, the silica gel used to purify this "dimer" was impregnated with triethylamine and then the compound could then be purified by flash chromatography using this adsorbant. After purification compound **203** was found to be reasonably stable, and could be stored for extended periods under nitrogen at 0 °C.

---

* An analogous epimerization (*viz.* **141→140**) was carried out during work directed towards the synthesis of PSDP analogues (see **Scheme 4.5**, page 65).

A related coupling has recently been reported by Noheda *et al.*[170]

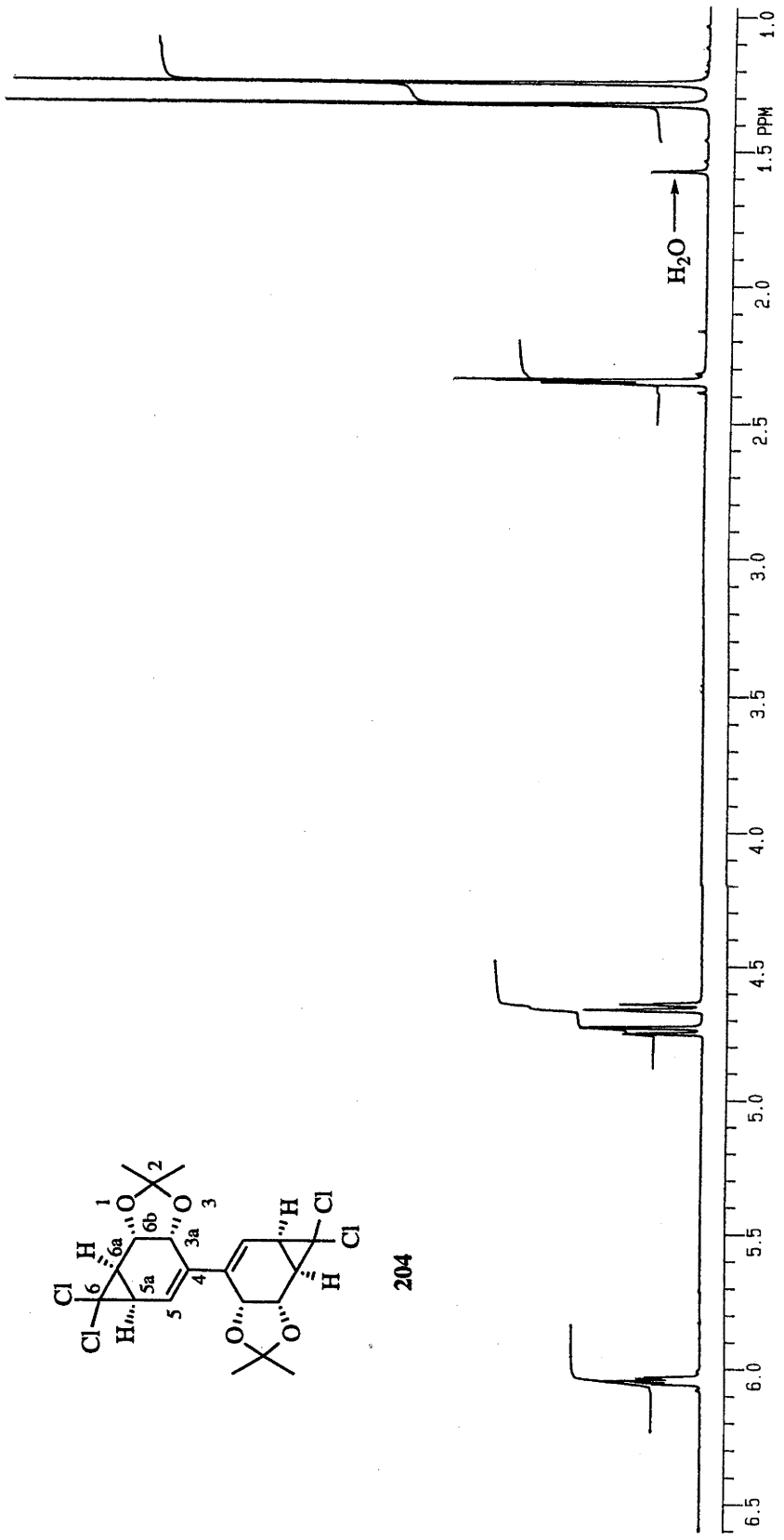
Treatment of *bis*-acetonide **203** with chloroform and aqueous sodium hydroxide in the presence of the phase-transfer catalyst triethylbenzylammonium chloride afforded, after flash column chromatography, a single *bis*-dichlorocarbene adduct, *viz.* compound **204** (29%). In the 300 MHz ^{1}H NMR spectrum of this product (**Figure 5.2**), the multiplet at δ 6.03 is attributed to the two magnetically equivalent alkene protons while doublets at δ 4.75 (J = 7.6 Hz) and 4.66 (J = 7.6 Hz) are assigned to the two pairs of oxymethine hydrogens within the molecule. In the upfield region of the spectrum the two pairs of cyclopropyl hydrogens resonate as a four-proton multiplet at δ 2.35. The remaining signals correspond to the two pairs of equivalent methyl group protons (δ 1.33 and 1.25) within structure **204**. In keeping with related conversions (see, for example, **101→100** on page 42), it was assumed that dichlorocarbene addition to compound **203** had occurred in a diastereofacially-selective manner to the less-hindered face of the two disubstituted double-bonds within *tetra*-ene **203**. Final proof of the structure of compound **204** followed from chemical correlation studies and a single-crystal X-ray analysis (see below).



14 (X=I) **202** **203** **204**

Scheme 5.4: *Reagents and Conditions*: (i) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (0.05 mole equiv.), 0 °C, 1 h, 82%. (ii) *t*-BuLi (2.0 mole equiv.), 0.2 h then $ZnCl_2$ (1.0 mole equiv.), -96 °C, 0.5 h then compound **202** (1.0 mole equiv.), $Pd(PPh_3)_4$ (0.05 mole equiv.), 2 h, 40%. (iii) $CHCl_3$, 50% w/v aq. NaOH (120 mole equiv.), TEBAC, 5 °C to 20 °C, 16 h, 29%.

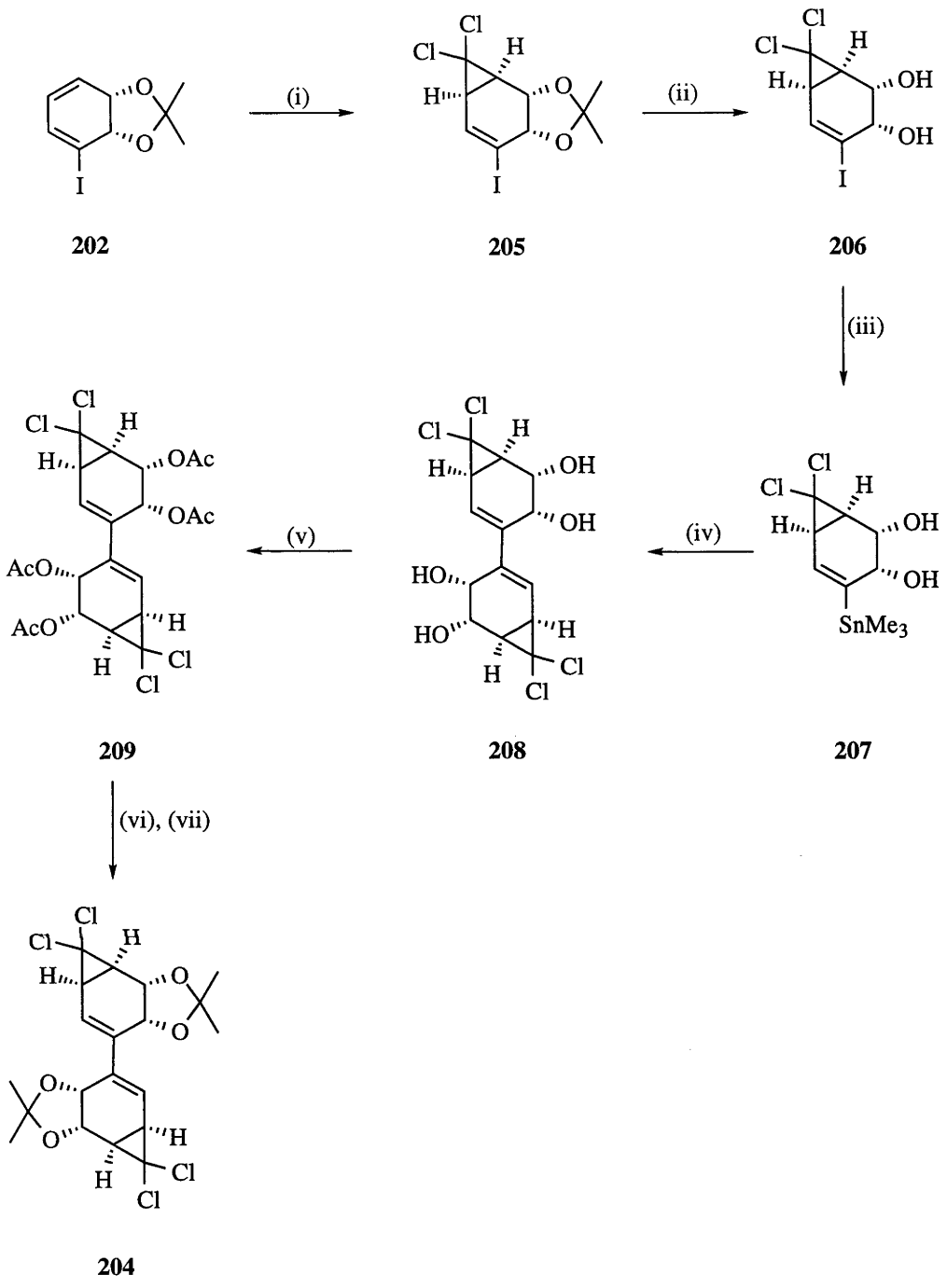
In an effort to confirm the structure assigned to compound **204**, a stepwise strategy was employed for its independent synthesis (**Scheme 5.5**). Thus, the acetonide derivative, **202**, of diol **14** (X=I) was subjected to reaction with dichlorocarbene



204

Figure 5.2: *300 MHz ^1H NMR Spectrum of Compound* **204**.

(Spectrum Recorded in $CDCl_3$ Solution)



Scheme 5.5: *Reagents and Conditions*: (i) $CHCl_3$, 50% w/v aq. NaOH (12.0 mole equiv.), TEBAC, 5 °C to 20 °C, 16 h, 78%. (ii) AcOH (60% aq.), 80 °C, 16 h, 81%. (iii) $(Me_3Sn)_2$ (1.07 mole equiv.), $Pd(PPh_3)_4$ (0.05 mole equiv.), THF, 50 °C, 16 h, 73%. (iv) compound **206** (0.90 mole equiv.), $Pd(PPh_3)_4$ (0.05 mole equiv.), 1,4-dioxane, 60 °C, 8 h. (v) Ac_2O, pyridine, 20 °C, 8 h, 74% from **206**. (vi) K_2CO_3 (6.0 mole equiv.), MeOH, reflux, 16 h. (vii) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (0.05 mole equiv.), 0 °C, 1 h, 84% from **209**.

(generated under phase-transfer conditions) and in this manner compound **205** was obtained in 78% yield and as a single diastereomer. Removal of the acetonide protecting group present within adduct **205** was effected using 60% aqueous acetic acid and

provided diol **206** in 81% yield. The latter compound was converted into the corresponding trimethylstannyl-derivative **207** (73%) by palladium-catalyzed coupling with hexamethylditin.[171] The next step in the reaction sequence required application of a homo- or cross-coupling protocol to produce the dimeric compound **208**. The transition-metal promoted coupling reactions of organic halides with organostannanes (Stille cross-coupling), organoboranes (Suzuki cross-coupling) or organic zinc species (Negishi cross-coupling) represent some of the most attractive methods for the creation of sp^2 to sp^2 carbon bond linkages because such conversions can normally be achieved under mild conditions and in high yield.[172] Indeed, when the alkenyl iodide **206** was reacted with the stannane **207** under classical Stille cross-coupling conditions the *tetra*-ol species **208** was obtained. Because of its poor solubility in a wide range of solvents, this product was extremely difficult to handle so, for the purposes of purification and characterization, it was immediately converted into the corresponding *tetra*-acetate derivative **209** (74% from **206**) under standard conditions. All spectoscopic data obtained on this latter material were in full accord with the assigned structure but final confirmation of its structure followed from a single crystal X-ray analysis of this material (**Figure 5.3**).

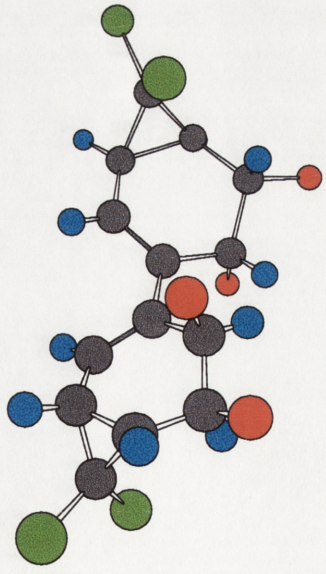


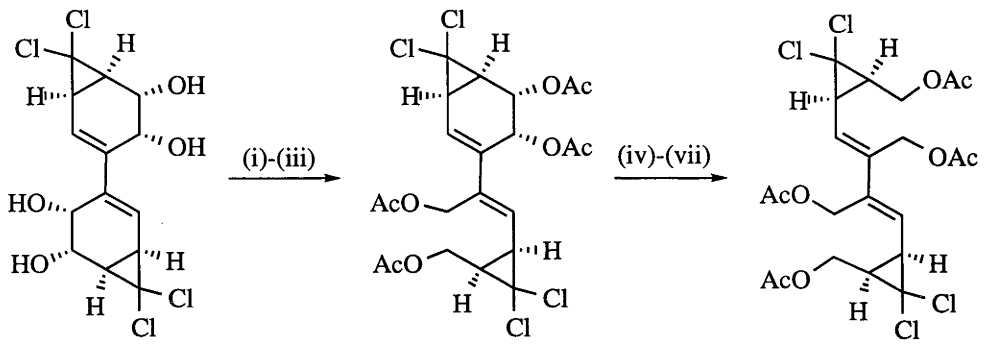
Figure 5.3: *CS Chem3D Pro™ Drawing of Compound* **209** *Generated Using Data Derived From an X-ray Crystallographic Study (Acetyl Groups Omitted for Clarity).*

The acquisition of compound **209** allowed for the conduct of the chemical correlation study alluded to earlier. Thus, base-catalyzed hydrolysis of the acetate groups present within compound **209** was effected with potassium carbonate in methanol and resulted in its smooth conversion into the highly insoluble *tetra*-ol **208**. The latter material was immediately treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid monohydrate to afford, after flash chromatography, *bis*-acetonide **204** (84% from **209**), which was identical, in all respects, with the material obtained earlier (see **Scheme 5.4**, page 91).

Various attempts to effect cyclopropanation of the double-bonds within dienes **204** and **208** proved unsuccessful. On the basis that the inductive-electron withdrawing effects of the chlorine atoms within dienes **204** and **208** might be deactivating the double-bonds towards electrophilic cyclopropanation, methods for the reductive dechlorination of these compounds were sought. To these ends, the *tetra*-ol **208** was subjected to several different types of dissolving metal reductions but in each case only starting material was returned. This outcome is probably the result of formation of insoluble polyalkoxide salts under the reduction conditions being employed. While it seemed as though reductive dechlorination of the corresponding *bis*-acetonide, **204**, could circumvent such problems, the dechlorinated material so-formed was exceptionally acid-sensitive and could not be deprotected under normal conditions used to remove acetonide protecting groups.

In a final attempt to set up favourable cyclopropanation conditions, efforts were made to convert compound **208** into acyclic congenor **211** on the basis that the double-bonds within the latter compound, or the corresponding *tetra*-ol, might be more susceptible to Simmons-Smith type cyclopropanation reactions (**Scheme 5.6**). To these ends *tetra*-ol **208** was treated with sodium metaperiodate, and the resulting product (which proved to be a dialdehyde-see below) was then reduced with sodium borohydride to give the unsymmetrical mono-ring opened adduct, which was characterized as the corresponding *tetra*-acetate **210**. In the 300 MHz ^{1}H NMR spectrum of the latter product, the doublets at δ 6.15 (J = 3.1 Hz) and 5.72 (J = 3.1 Hz) are assigned to the two different alkene

hydrogens. Six oxymethine signals were observed between δ 4.95 and 4.07, and in the more upfield region of the spectrum four distinct resonances due to the cyclopropyl hydrogens appear between δ 2.70 and 2.12. The remaining signals (δ 2.08 and 2.05) correspond to the four acetoxy-methyl groups present within compound **210**.

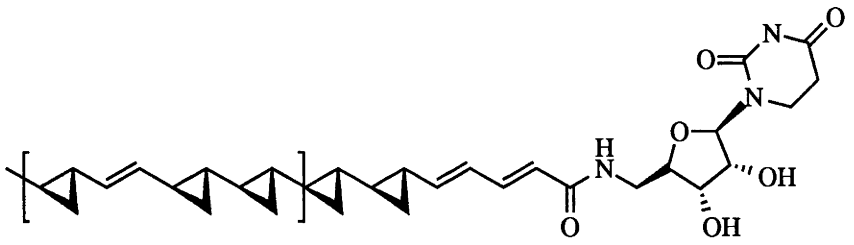


208 **210** **211**

Scheme 5.6: *Reagents and Conditions*: (i) $NaIO_4$ (3.0 mole equiv.), THF/H_2O (1:1), 5 °C, 1 h. (ii) $NaBH_4$ (22.0 mole equiv.), THF/MeOH (10:1), 5 °C, 8 h. (iii) Ac_2O, pyridine, 20 °C, 8 h, 50% from **208**. (iv) K_2CO_3 (18.0 mole equiv.), MeOH, reflux, 16 h. (v) $NaIO_4$ (8.0 mole equiv.), THF/H_2O (1:1), 5 °C, 1 h. (vi) $NaBH_4$ (8.0 mole equiv.), THF/MeOH (10:1), 5 °C, 8 h. (vii) Ac_2O, pyridine, 20 °C, 8 h, 60% from **210**.

Conversion, *via* hydrolytic removal of the acetate groups, of compound **210** into the corresponding *tetra*-ol and subjection of this latter material to reaction with sodium metaperiodate gave the expected dialdehyde/diol. This last compound was then reduced with sodium borohydride to give the expected *tetra*-ol which was characterized as the corresponding *tetra*-acetate **211** (60% from **210**). In the downfield region of the 300 MHz ^1H NMR spectrum of product **211** a two-proton doublet (J = 7.9 Hz) was observed at δ 6.00 and this is assigned to the two equivalent alkene hydrogens. The two-proton singlet at δ 4.86 is attributed to the allylic oxymethine protons, while the doublet (J = 7.9 Hz) at δ 4.14 is attributed to the oxymethine protons adjacent to the cyclopropyl moiety. Two two-proton cyclopropyl resonances were observed at δ 2.75 (dd, J = 7.8 and 1.6 Hz) and 2.85 (ddd, J = 7.8, 7.5 and 7.3 Hz) and the remaining signals (δ 2.09 and 2.06) correspond to the two types of acetoxy-methyl groups present within compound **211**.

All attempts to effect cyclopropanation of compound **211** under a variety of conditions were unsuccessful. In all cases starting material was recovered. Difficulties associated with cyclopropanating the double-bonds in compounds such as **208** and **211** prompted a consideration of exploiting this behaviour and targeting the synthesis of the left-hand ends of FR-900848 (**180**) and U-106305 (**181**), both of which contain the same combination of terminal methyl group and tri-cyclopropyl array interrupted by a carbon-carbon double-bond (**Figure 5.4**). Efforts directed towards these ends, which are detailed in the following section, seemed worthwhile because both Barrett[157] and Charette[163] had experienced considerable difficulties in establishing the terminal methyl group associated with these polycyclopropane arrays.



180 (FR-900848)

181 (U-106305)

Figure 5.4

5.5 Chemoenzymatic Syntheses of Derivatives of the Cyclopropane-Containing Terminus Associated with FR-900848 and U-106305

It was envisaged that the microbially-derived *cis*-1,2-dihydrocatechol **16** could be exploited for the synthesis, in enantiopure form, of the *tri*-cyclopropyl array **212**. The relevant retrosynthetic analysis associated with the proposed study is outlined in **Figure 5.5**. Thus, it was expected that the tricyclopropane **213** could be constructed *via* oxidative cleavage of the *cis*-vicinal diol present within compound **214**. In principle, the aldehyde moieties within compound **213** could be deleted using

Wilkinson's catalyst[167] so as to provide target **212**. It was anticipated that two-fold cyclopropanation of compound **215** would provide target **214** and, in keeping with previous results (see above), it was anticipated that the cyclohexyl double-bond present within compound **215** would not engage in any cyclopropanation reaction. Compound **215** could, in turn, be derived from a Heck reaction between iodide **216** and (*E*)-2,4-pentadienoic acid or the corresponding methyl ester. Tricycle **216** should be readily obtained from compound **16**, which is the product from microbial oxidation of *p*-iodotoluene.*

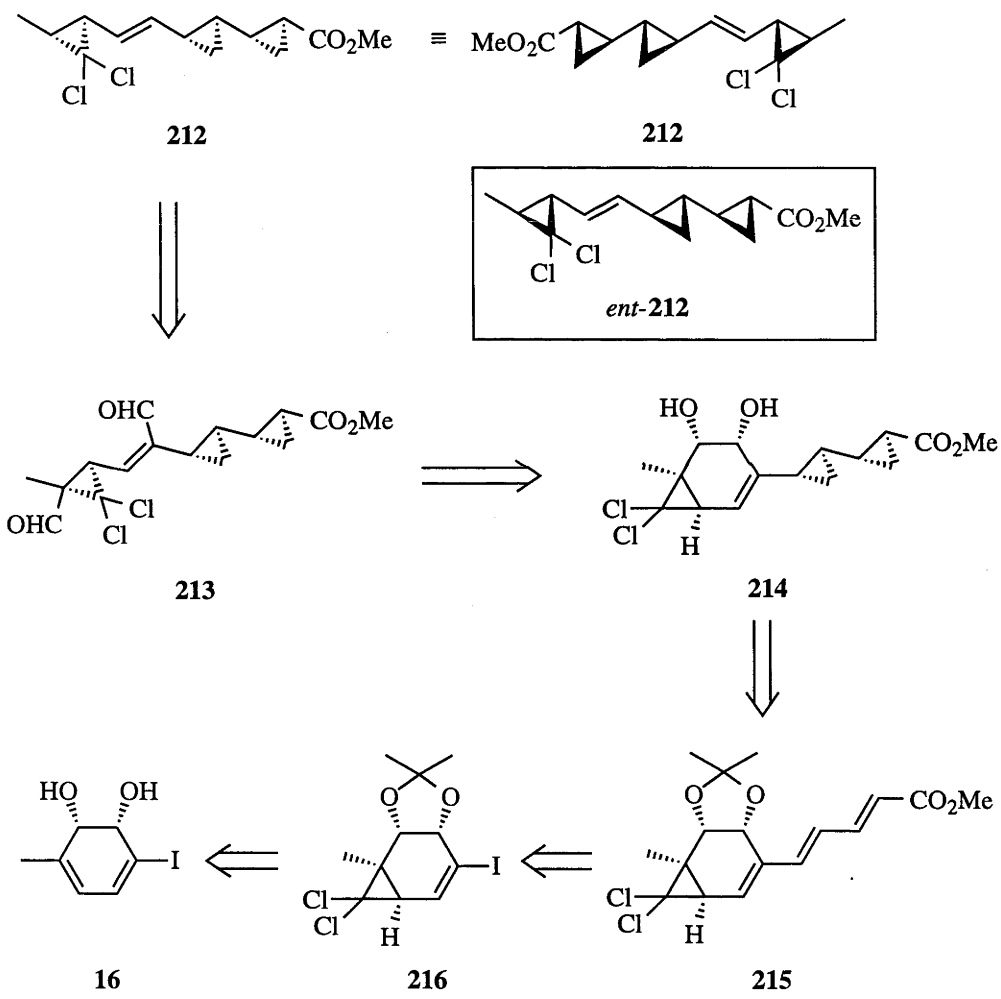
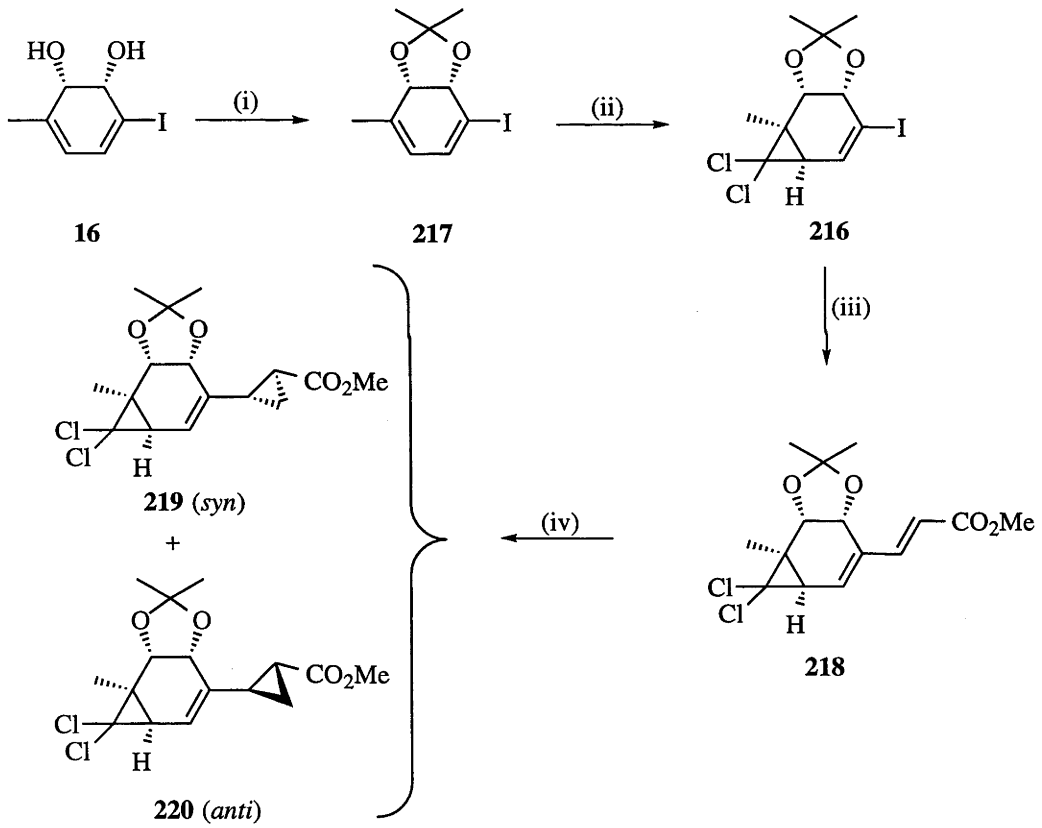


Figure 5.5: *Retrosynthetic Analysis of Tricyclopropane* **212** *Based Upon Using the* p-*Iodotoluene-Derived* cis-*1,2-Dihydrocatechol* **16** *as Starting Material.*

* It should be noted that compound **212** is in the opposite enantiomeric series to that required for the synthesis of the naturally occurring enantiomers of FR-900848 (**180**) and U-106305 (**181**). However, development of a synthesis of *ent*-**216** (or the corresponding diol) would make possible access to the correct enantiomeric series and thereby lead to the appropriate compound, *viz. ent*-**212**. This has been achieved (see pages 104-107).

In an effort to test the feasibility of the ideas enunciated in **Figure 5.5**, the acetonide derivative, **217**, of diol **16** was treated with dichlorocarbene to afford compound **216** (77%, **Scheme 5.7**). It should be noted that compound **216** is necessarily obtained in only *ca.* 80% ee because this is the enantiomeric excess associated with precursor **16** derived *via* microbial oxidation of *p*-iodotoluene. However, since compound **216** is a solid it could be recrystallised to constant melting point and $[\alpha]_D$. On the basis of doing this, it is assumed, that compound **216** and all of its derivatives are of >95% ee.[&] In an initial effort to examine the utility of Heck-type reactions[173] for replacing the iodine atom within compound **216** by an unsaturated side-chain that could be cyclopropanated, this material was subjected to reaction with methyl acrylate under

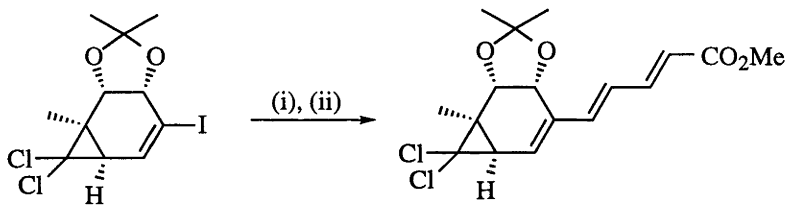


Scheme 5.7 *Reagents and Conditions*: (i) 2,2-dimethoxypropane, *p*-toluenesulfonic acid (0.05 mole equiv.), 0 °C, 1 h, 97%. (ii) $CHCl_3$, 50% w/v aq. NaOH (14.0 mole equiv.), TEBAC, 5 °C to 20 °C, 16 h, 77%. (iii) methyl acrylate (1.2 mole equiv.), PPh_3 (0.2 mole equiv.), K_2CO_3 (2.0 mole equiv.), Et_4NH_4Cl (1.0 mole equiv.), $Pd(OAc)_2$ (0.05 mole equiv.), DMF, 75 °C, 16 h, 78%. (iv) CH_2N_2 (excess), $Pd(OAc)_2$ (0.05 mole equiv.), 0 °C, 1 h, 86%.

[&] This assumption remains because no effort has been made to establish the enantiomeric purity of compound **216**.

standard Heck conditions. The diene-ester **218** (78%) thus obtained was cyclopropanated with diazomethane and palladium acetate[174] and an inseparable *ca.* 2.3:1 mixture of two diastereomers, **219** and **220** (86% combined yield), was thereby produced.[$] In keeping with expectation, no products arising from cyclopropanation of the internal olefin present within diene-ester **218** was observed.

The results just described prompted efforts to explore methods for the synthesis of derivatives of the left-hand terminus associated with polycyclopropanes FR-900848 and U-106305 (see **Figure 5.4**). To these ends, iodide **216** was subjected to a Heck reaction with (*E*)-2,4-pentadienoic acid[173] and the resulting triene acid treated with diazomethane so as to give the corresponding ester **215** (45% from **216**, **Scheme 5.8**). The former reaction was found, at times, to be low yielding, perhaps because of the propensity of (*E*)-2,4-pentadienoic acid to polymerize upon heating.[173] To

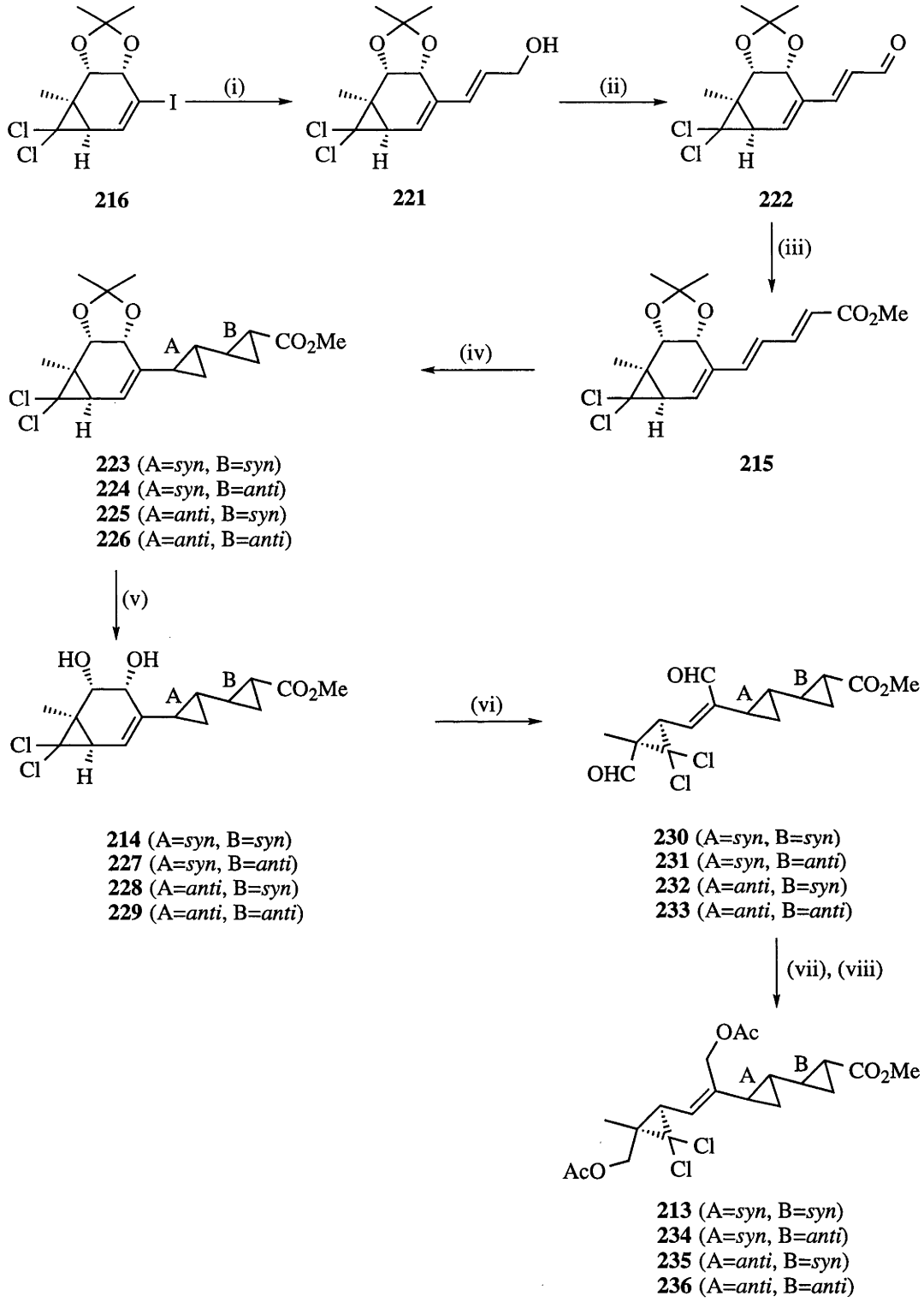


216 **215**

Scheme 5.8 *Reagents and Conditions*: (i) (*E*)-2,4-pentadienoic acid (1.25 mole equiv.), $Pd(OAc)_2$ (0.05 mole equiv.), PPh_3 (0.2 mole equiv.), K_2CO_3 (2.0 mole equiv.), Et_4NCl (1.0 mole equiv.), DMF, 75 °C, 16 h then CH_2N_2 (excess), Et_2O, 5 °C, 2 h, 45% from **216**.

circumvent such difficulties an alternative route to compound **215** was pursued, based upon the stepwise construction of the target molecule (**Scheme 5.9**). Thus, iodide **216** was subjected to a Stille-type cross-coupling reaction with the known (*E*)-tri-*n*-butyl-1-propen-3-ol stannane (prepared in three steps from propargyl alcohol)[176] to afford compound **221** (74%). Oxidation of this latter compound using tetrapropylammonium perruthenate with *N*-methylmorpholine-*N*-oxide as co-oxidant[177]

[$] The limited diastereoselectivities observed in this cyclopropanation reaction match those obtained when a chiral phenyloxazolidinone containing an α,β-unsaturated ester was cyclopropanated with diazomethane and palladium acetate.[175]



Scheme 5.9 *Reagents and Conditions*: (i) (*E*)-tri-*n*-butyl-1-propen-3-ol stannane (6.0 mole equiv.), THF, 50 °C, 16 h, 74%. (ii) NMO (2.0 mole equiv.), 4Å molecular sieves, TPAP (0.05 mole equiv.), CH_2Cl_2, 20 °C, 2 h, 74%. (iii) trimethylphosphonoacetate (1.5 mole equiv.), NaH (1.5 mole equiv.), THF, 50 °C, 2 h, 83%. (iv) CH_2N_2 (excess), Et_2O, 5 °C, 2 h, 86%. (v) AcOH (60% aq.), 80 °C, 16 h. (vi) $NaIO_4$ (8.0 mole equiv.), THF/H_2O (1:1), 5 °C, 1 h. (vii) $NaBH_4$ (8.0 mole equiv.), THF/MeOH (10:1), 5 °C, 8 h. (viii) Ac_2O, pyridine, 20 °C, 8 h, 67% from **223-226**. [See **Scheme 5.7** for structures that define the manner in which the *syn*- and *anti*-descriptors are employed here].

provided aldehyde **222**, which was subjected to a Horner-Wadsworth-Emmons olefination reaction.[178] In this manner, compound **215** was obtained in 83% yield.

Compound **215** was cyclopropanated with diazomethane in the presence of palladium acetate and in this manner a *ca.* 4:3:1:1 mixture[%] of the four possible products **223-226**, (86% combined yield) was obtained. The chromatographically least mobile of these diastereoisomers could be separated from the other three *via* semi-preparative normal-phase HPLC on silica. In the downfield region of the 300 MHz ^{1}H NMR spectrum of this single product (**Figure 5.6**) a one-proton doublet (J = 6.3 Hz) was observed at δ 5.42, and assigned to the alkenyl hydrogen. Two mutually coupled oxymethine protons were observed at δ 4.41 (d, J = 6.6 Hz) and δ 4.39 (d, J = 6.6 Hz), while the singlet at δ 3.66 is attributed to the methyl protons of the carbomethoxy group. The doublet (J = 6.3 Hz) at δ 1.82 is assigned to the cyclopropyl-hydrogen adjacent to the *gem*-dichloro cyclopropyl moiety. A three-proton singlet at δ 1.56 and a six-proton singlet at δ 1.39 account for the protons of the remaining three methyl groups. In the low-field region of the spectrum four signals, at δ 1.40, 1.10, 0.73 and 0.53, are observed and are assigned to the remaining eight cyclopropyl-hydrogens within this compound.

The acetonide groups within the *ca.* 4:3:1:1 mixture of diastereoisomers **223-226** were removed using aqueous acetic acid so as to afford the corresponding mixture of diols **214** and **227-229**. Treatment of these latter compounds with sodium metaperiodate then gave a mixture of unstable dialdehydes **230-233**, which were immediately reduced to the corresponding mixture of open-chain diols using sodium borohydride. The mixture of these latter compounds was acetylated under standard conditions to give the compounds **213** and **234-236** (67% from **223-226**), again as a *ca.* 4:3:1:1 mixture of diastereoisomers which were inseparable by various chromatographic techniques including semi-preparative HPLC. However, one of the four compounds must necessarily have the structure which corresponds to the left-hand end of both *ent*-FR-900848 (**180**) and *ent*-U-106305 (**181**).

[%] This ratio was determined by analytical gas chromatography. Injection temperature = 150 °C; final temperature = 300 °C; temperature gradient = 10 °C/min.

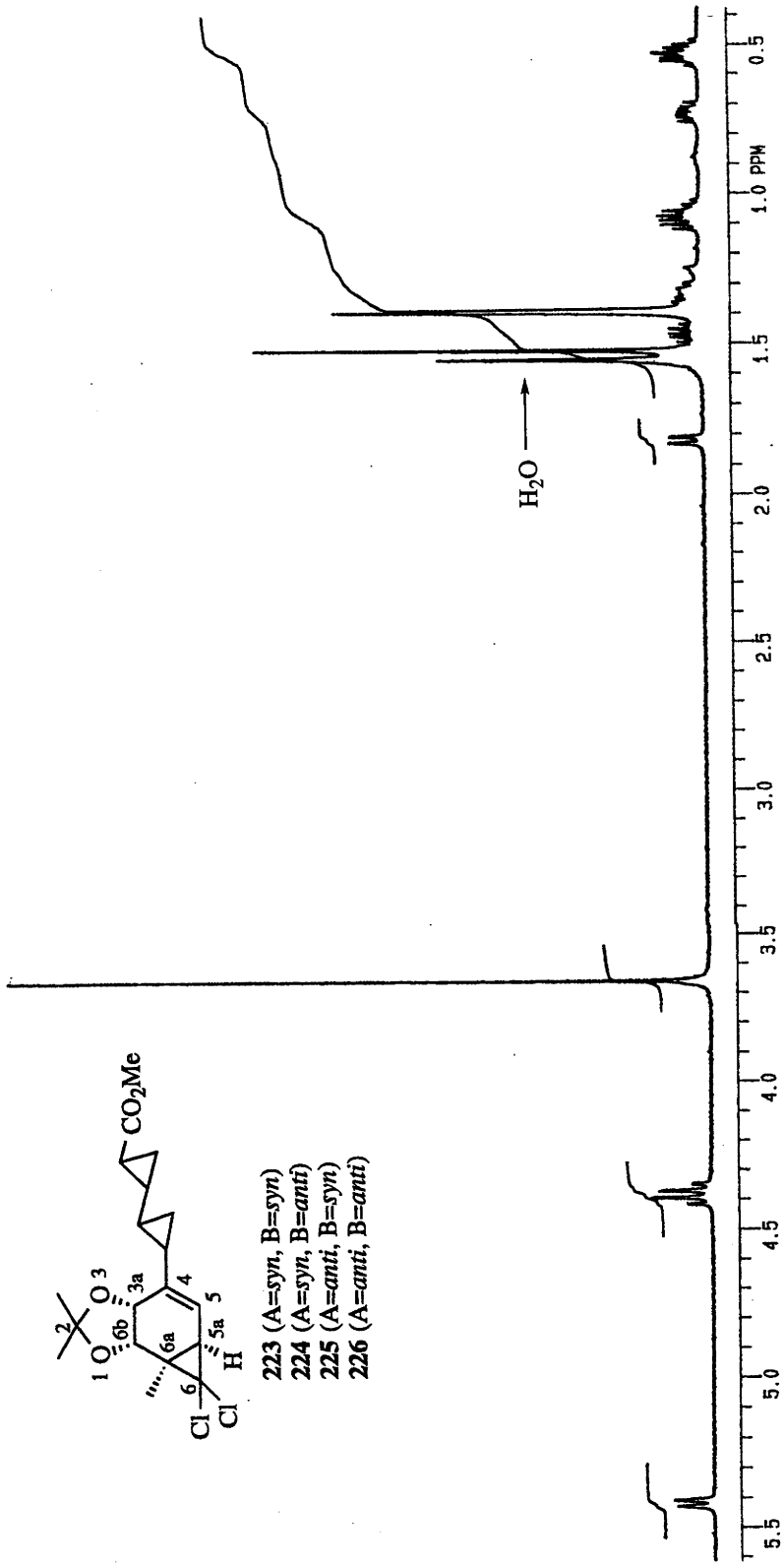
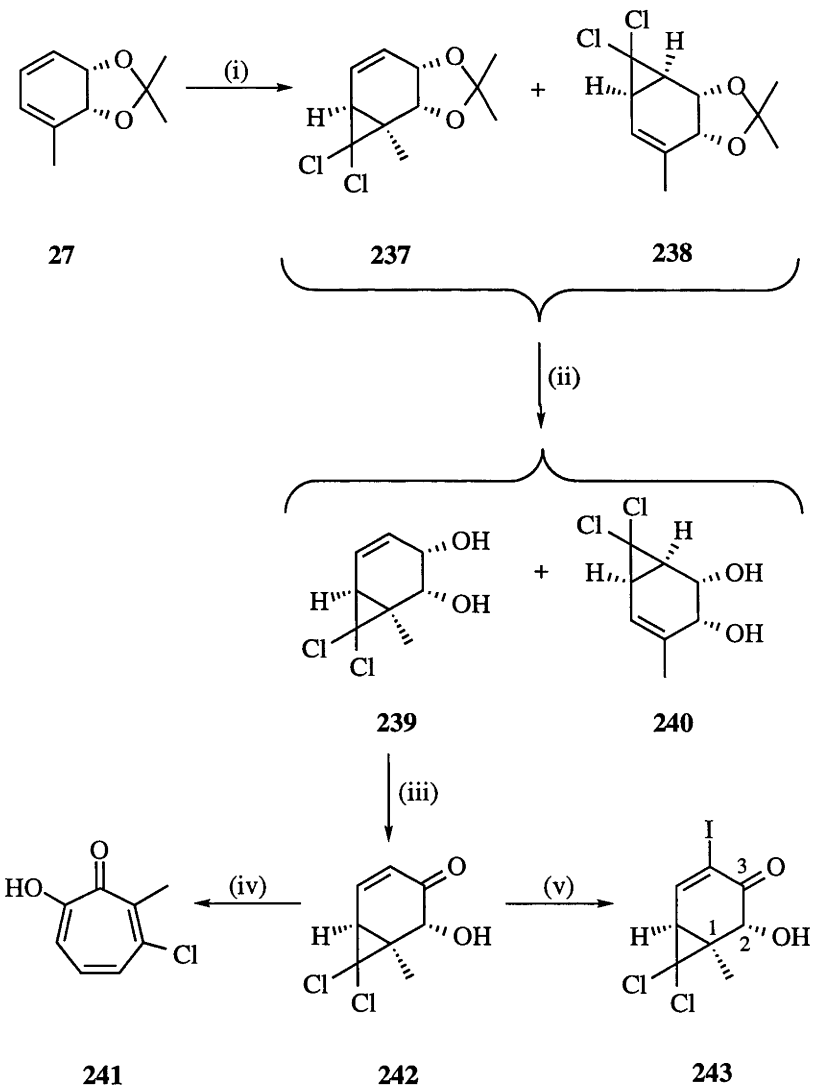


Figure 5.6: *300 MHz ^1H NMR Spectrum of the Single Diastereomer Separated from the Mixture of Compounds* **223-226** *by HPLC.*

(Spectrum Recorded in $CDCl_3$ Solution)

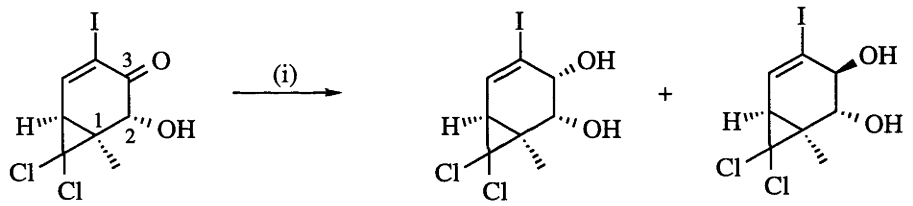
As noted earlier, the synthesis of *ent*-**216** would allow access, via the chemistry outlined above, to the natural enantiomeric series associated with these polycyclopropyl arrays. Consequently, some efforts were focussed on preparation of iodide *ent*-**216** from diol **17**. To these ends (**Scheme 5.10**), the readily available acetonide derivative,[75] **27**, of *cis*-1,2-dihydrocatechol **17** was treated with chloroform and aqueous sodium hydroxide in the presence of the phase-transfer catalyst triethylbenzylammonium chloride. As a result, a 1.2:1 mixture of cycloadducts **237** and **238** was obtained in 82% overall yield. These regioisomers could not be separated from one another by flash chromatography so the mixture was subjected to acid-



Scheme 5.10 *Reagents and Conditions*: (i) $CHCl_3$, 50% w/v aq. NaOH (12.0 mole equiv.), TEBAC, 5 °C to 20 °C, 16 h, 82%. (ii) AcOH (60% aq.), 80 °C, 16 h, 63%. (iii) DMSO (3.2 mole equiv.), oxalyl chloride (1.5 mole equiv.), NEt_3 (3.2 mole equiv.), CH_2Cl_2, -78 °C, 2.5 h, 65%. (iv) $CDCl_3$ (NMR tube), 20 °C, 12 h, 100%. (v) I_2 (4.2 mole equiv.), CCl_4/pyridine (1:1), 20 °C, 64%.

catalyzed hydrolysis of the acetonide protecting group. The resulting diols **239** and **240** were then readily separated by flash column chromatography[75] and the former product mono-oxidized under Swern[179] conditions to afford enone **242**. While this product was somewhat unstable, and often underwent a ring-expansion reaction with loss of HCl so as to give the troponoid **241**, careful iodination[180] of compound **242** under conditions defined by Johnson *et al.* provided iodide **243** in 64% yield after flash chromatography.

Diastereoselective 1,2-reduction of the enone moiety present within compound **243** so as to give the target *syn*-diol **244** proved to be anything but straightforward. Thus, reaction of enone **243** with a variety of reducing agents (**Table 5.1**) afforded mixtures of *syn*- and *anti*-diols **244** and **245**, with the *anti*-diol being the major product of reaction in most instances (**Scheme 5.11**, **Table 5.1**). For example, reduction of ketone **243** with zinc borohydride at -78 °C (**Entry 3**, **Table 5.1**) afforded a 4:96



243 **244** **245**

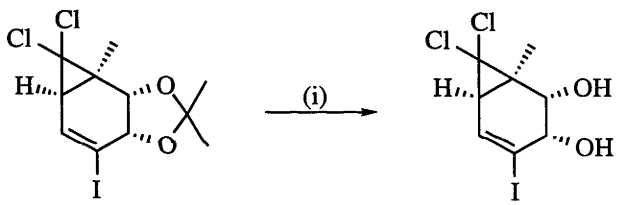
Scheme 5.11 *Reagents and Conditions*: (i) See **Table 5.1** (below).

Entry	Reducing Agent	Temp.	Time	Combined Yield	Ratio of products 244:245
1	$NaBH_4$	0 °C	8 hours	98 %	36:64
2	$NaBH_4$	-78 °C	8 hours	94 %	14:86
3	$ZnBH_4$	-78 °C	1 hour	93 %	4:96
4	$LiAlH_4$	0 °C	6 hours	86 %	3:97
5	DIBAL-H	0 °C	2.5 hours	92 %	37:63
6	DIBAL-H	-78 °C	2.5 hours	84 %	44:56

Table 5.1: *Results of Subjecting Acyloin* **243** *to 1,2-Reduction With a Variety of Hydride Donors.*

mixture of *syn*- and *anti*-diols **244** and **245**, which were only separable by preparative HPLC techniques. The observed preference for production of the *anti*-diol in these reduction processes probably derives from chelation of the reducing agent to the C-2 hydroxyl group with the result that the ensuing conjugate delivers hydride from the α-face of the molecule. Despite these unexpected results, a formal connection was made between diol **244** and its enantiomer *ent*-**244**.

In order to confirm the structure of diol **244**, its enantiomer was also prepared. Thus, hydrolysis of the acetonide group present within compound **216** afforded diol *ent*-**244** (**Scheme 5.12**), and the spectral data obtained for this latter compound were identical to those obtained for compound **244**. The specific rotation observed for the sample of compound *ent*-**244** {$[\alpha]_D^{20}$ - 57.2 ° (*c* 3.2, chloroform)} prepared by the route just described was of essentially the same magnitude but opposite sign to compound **244** {$[\alpha]_D^{20}$ + 54.0 ° (*c* 1.0, chloroform)}.



216 *ent*-**244**

Scheme 5.12 *Reagents and Conditions*: (i) AcOH (60% aq.), 80 °C, 16 h, 76%.

5.6 Conclusion

The reactions described in this chapter reveal the scope and limitations associated with preparing polycyclopropyl substructures associated with the natural products FR-900848 (**180**) and U-106305 (**181**) using *cis*-1,2-dihydrocatechols as starting materials. A series of hitherto unknown polycyclopropanes have been prepared from *cis*-1,2-dihydrocatechols **14** (X=I) and **16**. Further work in this area would seem to be warranted.

CHAPTER SIX

Experimental Section

6.1 General Experimental Procedures

Instrumentation and Equipment:

Proton (^1H), carbon (^{13}C) and phosphorous (^{31}P) NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 300 MHz for proton, 75.4 MHz for carbon and 121.4 MHz for phosphorous, respectively. Deuterochloroform ($CDCl_3$) was used as solvent unless otherwise indicated. Chemical shifts are recorded as δ values in parts per million (ppm), the nominal standard being tetramethylsilane (TMS) (0.00 ppm). Proton spectra recorded in deuterochloroform were referenced against residual $CDCl_3$ (7.26 ppm), while the central peak (77.0 ppm) of the $CDCl_3$ triplet was used as the internal reference for carbon spectra. In those cases where d_6-acetone [$(CD_3)_2CO$] was used as solvent, carbon spectra were referenced to the central peak (29.2 ppm) of the $(CD_3)_2CO$ heptet. Data are recorded as follows: chemical shift (δ), relative integral, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets *etc.*, br=broad), coupling constant(s) (*J* Hz). Distortionless enhancement by polarization transfer (DEPT), attached proton test (APT) and heteronuclear correlation (HETCOR) techniques were employed for the assignment of NMR spectra.

Infrared spectra (ν_{max}) were recorded on either a Perkin-Elmer 1800 Fourier Transform Infrared Spectrophotometer or a Perkin-Elmer 683 Infrared Spectrophotometer. Samples were analyzed as either KBr discs (for solids) or as thin liquid films (for oils) on potassium bromide (KBr) plates.

Low and high resolution mass spectra were recorded on a VG Micromass 7070F double-focussing mass spectrometer using (unless otherwise stated) positive ion electron impact (EI, 70 eV electron beam) techniques at the voltages indicated. Mass spectral data are listed as mass-to-charge ratio (*m/z*), assignment (where possible) and relative intensity (% of base peak).

Optical rotations {$[\alpha]_D$} were recorded on a Perkin-Elmer 241 polarimeter using (unless otherwise stated) spectroscopic grade chloroform or acetone as solvent at the temperature and concentration (*c*) (g/100 mL) indicated.

Melting points were recorded on a Reichert Hot-Stage microscope and are uncorrected.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit on a Carbo Erba EA 1106 CHN-O Elemental Analyzer. A titrometric method, using mercury nitrate, was employed for halogen analysis.

Ozonolyses were performed using a Wallace and Tiernan Ozonator with the oxygen flow rate and power adjusted to approximately 25 L/h and 200 V, respectively.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 GF_{254} plates (supplied by Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by treatment with a reagent solution [either anisaldehyde/sulfuric acid/ethanol (2:5:93) dip, phosphomolybdic acid/ethanol (8 g/200 mL) dip or phosphomolbdic acid/ceric (IV) sulfate/sulfuric acid/water (37.5 g:7.5 g:37.5 mL:720 mL) dip] followed by heating. Flash chromatography was conducted according to the method of Still[181] using the analytical reagent (AR) grade solvents indicated.

High performance liquid chromatography (HPLC) was conducted on a Waters μ-Porasil™ semi-preparative silica column (7.8 x 300 mm) connected to an ISCO Model 2350 pump. The peaks were detected using an ERMA ERC-7512 refractive index detector connected to a Spectra-Physics SP4270 reporting integrator.

Gas chromatography (GC) was performed on either a Varian 3400 Gas Chromatograph fitted with a SGE Cydex-B chiral capillary column (25 m x 0.22 mm internal diameter, film thickness = 25 micron) or a Varian Vista Series Gas Chromatograph fitted with a SGE BPX5 silica capillary column (25 m x 0.22 mm internal diameter, film thickness = 25 micron). The peaks were detected using a flame-ionization detector and helium was the carrier gas in all cases (flow rate *ca.* 35 cm/sec). Specific temperature programs are detailed for each individual case.

Materials and Methods:

All *cis*-1,2-dihydrocatechols were generously provided by Genencor International Inc. (Palo Alto, CA) and used as obtained with the exception of compounds **16** and **17.** (For general procedures for the extraction of (1*S*,2*R*)-*cis*-3-methyl-3,5-cyclohexadiene-1,2-diol (**17**) and (1*S*,2*S*)-*cis*-3-iodo-5-methyl-3,5-cyclohexadiene-1,2-diol (**16**) from their corresponding fermentation broths see pages **136** and **182**, respectively).

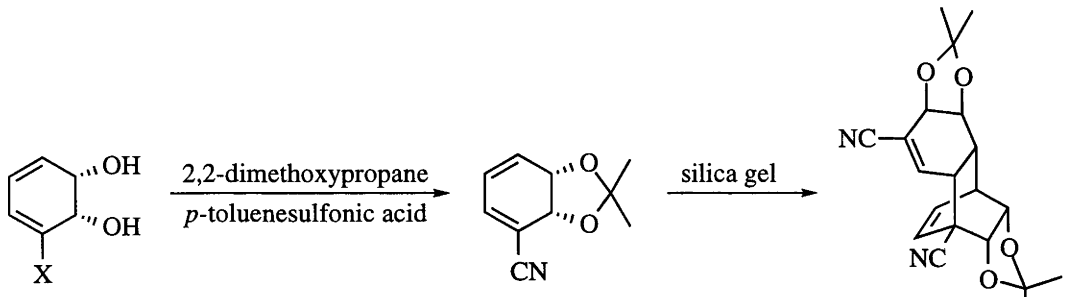
Many reagents and starting materials are available from the Sigma-Aldrich-Fluka Chemical Company and were used as supplied. Ethereal diazomethane was prepared according to the method of de Boer and co-workers.[182] Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reaction solvents and reagents were purified according to established procedures.[183] The concentrations of alkyl lithium solutions obtained from Aldrich were determined by titration with *sec*-butanol (1.0 M solution in toluene) using 1,10-phenanthroline as indicator.[184] Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled, under nitrogen, from sodium benzophenone ketyl, while methanol and ethanol were distilled from their respective magnesium alkoxide salts. Benzene (C_6H_6), toluene, dichloromethane (CH_2Cl_2) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride. Pyridine and triethylamine (NEt_3) were distilled from potassium hydroxide pellets. Dimethyl sulfoxide (DMSO) was distilled at reduced pressure (*ca.* 15 mmHg) and the initial 20% of the distillate was discarded before collection began. Sodium iodide was dried overnight under high vacuum (0.5 mmHg) at 70 °C then cooled and stored in a desiccator. 4 Å Molecular sieves were dried by heating in a 1000 Watt microwave oven (running at full power for 0.1 h). The cooled sieves were then transferred to an oven dried container and sealed.

Reactions employing air- and/or moisture-sensitive reagents were carried out under an atmosphere of dry, oxygen-free nitrogen in oven- or flame-dried apparatus. Solutions were concentrated under reduced pressure on a Büchi R-114 rotary

evaporator. When reactions were conducted at, or below, 0 °C the internal temperature was monitored using an alcohol thermometer.

6.2 Experimental Details Associated with Work Described in Chapter Two

(1*S*,2*R*,5*R*,6*S*,7*S*,8*S*,9*S*,10*R*)-1,4-Dicyano-5,6:9,10-*bis*-(isopropylidenedioxy)tricyclo[6.2.2.0]dodeca-3,11-diene (64).



14 (X=CN) **63** **64**

p-Toluenesulfonic acid monohydrate (318 mg, 1.60 mmol) was added, in one portion, to a magnetically stirred solution of (1*S*,2*R*)-*cis*-3-cyano-3,5-cyclohexadiene-1,2-diol (**14**, X=CN) (1.21 g, 8.75 mmol) in dry acetone (20 mL) and 2,2-dimethoxypropane (10 mL, 16.2 mmol) maintained at *ca.* -10 °C (salt-ice bath) under a nitrogen atmosphere. After 0.5 h the reaction mixture was treated with triethylamine (1.0 mL) then concentrated under reduced pressure. The residue thus obtained was partitioned between Et_2O (50 mL) and water (30 mL). The separated aqueous phase was extracted with Et_2O (2 x 50 mL) then the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.3), a white solid. Recrystallization (hexane/EtOAc) of this material then gave compound **64** [834 mg, 54% from **14** (X=CN)] as colourless needles, m.p. 252-253 °C (lit.[76] m.p. 211 °C).

^{1}H NMR (300 MHz) δ: 6.72 (1H, d, J = 5.7 Hz), 6.14 (1H, apparent t, J = 8.4 Hz), 6.00 (1H, d, J = 8.4 Hz), 4.46 (2H, s), 4.24 (1H, d, J = 3.3 Hz), 4.18 (1H, d, J = 4.5 Hz), 3.04 (1H, d, J = 6.3 Hz), 2.86-2.81 (1H, m), 2.42 (1H, d, J = 8.4 Hz), 1.40 (3H, s), 1.36 (3H, s), 1.33 (3H, s), 1.30 (3H, s).

^{13}C NMR (75.4 MHz) δ: 141.2 (CH), 130.9 (CH), 129.2 (CH), 120.0 (C), 117.6 (C), 116.8 (C), 111.2 (C), 109.9 (C), 79.8 (CH), 77.9 (CH), 76.7 (CH), 69.3 (CH), 44.1 (C), 39.6 (CH or CH_3), 37.9 (CH or CH_3), 33.2 (CH or CH_3), 28.2 (CH or CH_3), 26.7 (CH or CH_3), 25.6 (CH or CH_3), 25.4 (CH or CH_3).

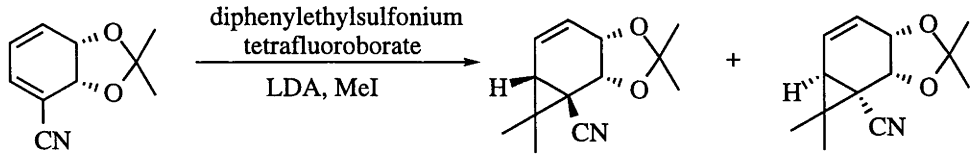
IR ν_{max} 2998, 2982, 2936, 2924, 2882, 2246, 2216, 1650, 1557, 1255 cm^{-1}

EIMS (70eV) *m/z* 354 ($M^{+\cdot}$, 7), 339 [$(M-H_3C\cdot)^+$, 84], 281 (100), 238 (52), 221 (73), 209 (48), 193 (52), 120 (66), 100 (89).

Elemental Analysis Found: C, 67.67; H, 6.62; N, 7.76; $C_{20}H_{22}N_2O_4$ requires: C, 67.78; H, 6.26; N, 7.90%.

Optical Rotation $[\alpha]_D^{20}$ + 105.4 ° (*c* 3.8, $CHCl_3$); {lit.[76] $[\alpha]_D^{20}$ + 110.9 ° (*c* 0.4, $CHCl_3$)}.

(3a*S*,5a*S*,6a*S*,6b*R*)-2,2,6,6-Tetramethyl-3a,6,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (65) and (3a*S*,5a*R*,6a*R*,6b*R*)-2,2,6,6-Tetramethyl-3a,6,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (66).

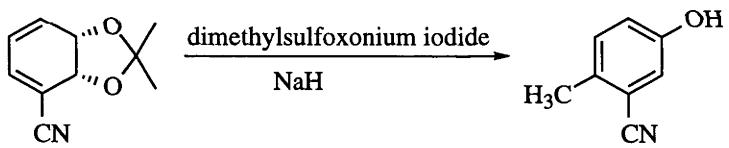


63 **65** **66**

Lithium diisopropylamine (1.6 mL of a 0.69 M solution in THF, 1.09 mmol) was added, dropwise, to a magnetically stirred suspension of diphenylethylsulfonium tetrafluoroborate[78] (299 mg, 0.99 mol) in dry CH_2Cl_2 (65 μL, 1.00 mmol), dry THF (5 mL) and dry DME (5 mL) maintained at -78 °C (acetone/dry-ice slush bath) under a nitrogen atmosphere. After stirring for 0.75 h at -80 °C to -70 °C methyl iodide (66 μL, 1.05 mmol) was added, dropwise, to the reaction mixture and the resulting solution stirred at -70 °C for 2 h. A further aliquot of lithium diisopropylamine (1.6 mL of a 0.69 M solution in THF, 1.09 mmol) was then added and after 1.25 h a solution of

compound **63** (172 mg, 0.97 mmol) in dry THF (0.5 mL) was added to the by now orange-coloured reaction mixture. The solution thus obtained was warmed to 18 °C over 2 h then diluted with water (10 mL) and Et_2O (50 mL). The separated aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide a pale-yellow oil which was subjected to flash chromatography (2:1 hexane/EtOAc elution). Concentration of the appropriate fractions (R_f 0.7) then gave a *ca.* 2:1 mixture (as judged by ^1H NMR analysis) of compounds **65** and **66** (140 mg, 66%) as a clear, colourless oil. All attempts to separate the components of this mixture failed but comparison of the ^1H NMR spectrum of this material with the analogous spectra of authentic samples of compounds **65** and **66** (see pages 119 and 120), prepared as described below, left little doubt as to the nature of the materials produced by the process described here.

3-Hydroxy-6-methylbenzenenitrile (70).



63 **70**

Trimethyloxosulfonium iodide[80] (285 mg, 1.30 mmol) was added, in portions, to a magnetically stirred suspension of sodium hydride (50 mg of a 60% dispersion in mineral oil, 1.24 mmol) (which was freed of oil by washing several times in anhydrous hexane) in dry DMSO (4 mL) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After 0.5 h a solution of diene **63** (200 mg, 1.13 mmol) in dry THF (2 mL) was added dropwise. The by now purple-coloured reaction mixture was stirred at 18 °C for 2 h then diluted with water (20 mL) and Et_2O (100 mL). The separated aqueous phase was extracted with Et_2O (1 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The

material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), compound **70** (114 mg, 76%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 7.18 (1H, d, *J* = 8.4 Hz), 7.10 (1H, d, *J* = 1.8 Hz), 7.01 (1H, dd, *J* = 8.4 and 1.8 Hz), 6.10 (1H, bs), 2.46 (3H, s).

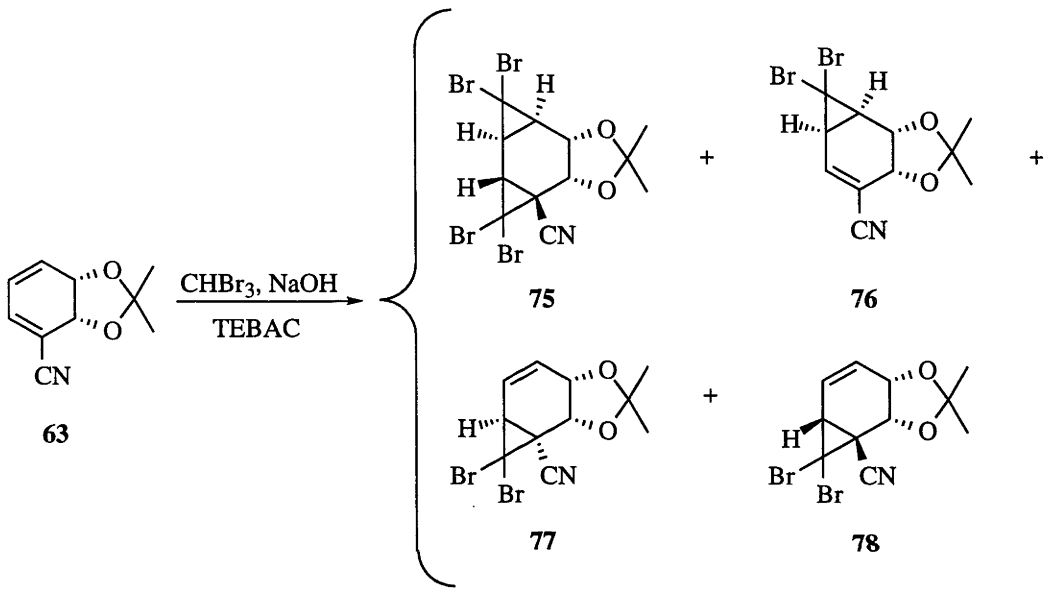
^{13}C NMR (75.4 MHz) δ: 154.2 (C), 134.3 (C), 131.9 (CH), 121.2 (CH), 118.9 (CH), 118.2 (C), 112.9 (C), 19.7 (CH_3).

IR ν_{max} 3327, 2922, 2239, 1622, 1579, 1507, 1298 cm^{-1}

EIMS (70eV) *m/z* 133 ($M^{+\cdot}$, 100), 119 (93), 106 (27), 91 (24), 77 (32).

HRMS Found $M^{+\cdot}$, 133.0527 C_8H_7NO requires $M^{+\cdot}$, 133.0527.

(3a*R*,3b*S*,4a*R*,4b*R*,5a*R*,5b*S*)-4,4,5,5-Tetrabromohexahydro-2,2-dimethyldicyclopropa[*e*,*g*]-1,3-benzodioxolo-3b(3a*H*)-carbonitrile (75), (3a*R*,5a*R*,6a*R*,6b*S*)-6,6-Dibromo-2,2-dimethyl-3a,5a,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-4(5a*H*)-carbonitrile (76), (3a*S*,5a*S*,6a*R*,6b*R*)-6,6-Dibromo-2,2-dimethyl-3a,5a,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzo-dioxolo-6a(5a*H*)-carbonitrile (77) and (3a*S*,5a*R*,6a*S*,6b*R*)-6,6-Dibromo-2,2-dimethyl-3a,5a,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (78).



Sodium hydroxide (30.25 mL of a 50% w/w aqueous solution, 380 mmol) was added, dropwise, to a magnetically stirred solution of compound **63** (11.0 g, 62.1 mmol), bromoform (27.5 mL, 313.5 mmol) and benzyltriethylammonium chloride (205 mg, 0.88 mmol) in dry benzene (220 mL) maintained at 5 °C (ice-bath). The resulting brown-coloured reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (300 mL) and water (270 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded three fractions, A-C.

Concentration of fraction A (R_f 0.8) yielded a white solid. Recrystallization (hexane/$CHCl_3$) of this material gave compound **75** (1.50 g, 5%) as colourless prisms, m.p. 219-220 °C.

^{1}H NMR (300 MHz) δ: 4.90 (1H, d, *J* = 8.4 Hz), 4.48 (1H, d, *J* = 8.4 Hz), 2.75 (1H, s), 2.35 (2H, m), 1.58 (3H, s), 1.39 (3H, s).

^{13}C NMR (75.4 MHz) δ: 119.6 (C), 110.4 (C), 72.7 (CH), 68.8 (CH), 38.3 (CH or CH_3), 32.2 (CH or CH_3), 27.8 (CH or CH_3), 25.2 (C), 25.1 (C), 24.9 (CH or CH_3), 22.6 (CH or CH_3), (one signal due to a quaternary carbon not observed).

IR ν_{max} 3043, 3015, 2992, 2916, 2224, 1382 cm^{-1}.

EIMS (70eV) *m/z* 507, 505, 503, 501 [$(M\text{-}H_3C\cdot)^+$, 10, 20, 28, 19], 446 (8), 381 (11), 364 (19), 274 (57), 100 (100).

Elemental Analysis Found: C, 27.41; H, 1.89; Br, 61.37; N, 2.35; $C_{12}H_{11}Br_4NO_2$ requires: C, 27.67; H, 2.13; Br, 61.21; N, 2.69%.

Optical Rotation $[\alpha]_D^{20}$ - 39.5 ° (*c* 1.0, $CHCl_3$).

Concentration of fraction B (R_f 0.7) yielded a white solid comprised of a *ca.* 4.4:1 mixture (as determined by ^{1}H NMR analysis) of compounds **76** and **77**. Recrystallization (hexane/EtOAc) of this material yielded compound **76** (5.90 g, 27%) as colourless prisms, m.p. 205-206 °C.

^{1}H NMR (300 MHz) δ: 6.83 (1H, d, *J* = 5.7 Hz), 4.74 (1H, d, *J* = 6.6 Hz), 4.49 (1H, d, *J* = 5.7 Hz), 2.58 (2H, m), 1.43 (3H, s), 1.40 (3H, s).

^{13}C NMR (75.4 MHz) δ: 139.0 (CH), 116.9 (C), 114.8 (C), 110.9 (C), 70.1 (CH), 69.3 (CH), 31.5 (CH or CH_3), 29.7 (C), 28.5 (CH or CH_3), 27.5 (CH or CH_3), 25.8 (CH or CH_3).

IR ν_{max} 2991, 2241, 1456, 1381, 1059 cm^{-1}.

EIMS (70eV) *m/z* 352, 350, 348 ($M^{+\cdot}$, 0.5, 0.7, 0.5), 337, 335, 333 [$(M\text{-}H_3C\cdot)^+$, 6, 8, 6], 290 (34), 274 (55), 210 (100), 182 (48), 103 (77).

Elemental Analysis Found: C, 38.14; H, 2.96; Br, 45.81; N, 4.06; $C_{11}H_{11}Br_2NO_2$ requires: C, 37.85; H, 3.18; Br, 45.79; N, 4.01%.

Optical Rotation $[\alpha]_D^{20}$ -96.7 ° (*c* 2.9, $CHCl_3$).

Recrystallization (hexane/Et_2O) of the solid obtained from concentration of the mother liquors associated with the recrystallization described above yielded compound **77** (6.80 g, 31%) as colourless prisms, m.p. 100-101 °C.

^{1}H NMR (300 MHz) δ: 6.03-5.97 (2H, m), 4.60 (1H, d, *J* = 7.2 Hz), 4.51 (1H, m), 2.78 (1H, d, *J* = 5.4 Hz), 1.45 (3H, s), 1.41 (3H, s).

^{13}C NMR (75.4 MHz) δ: 129.4 (CH), 121.1 (CH), 117.5 (C), 111.4 (C), 71.0 (CH), 69.4 (CH), 35.3 (CH), 32.0 (C), 27.7 (CH_3), 27.1 (C), 26.1 (CH_3).

IR ν_{max} 2991, 2936, 2241, 1381, 1220, 1059 cm^{-1}.

EIMS (70eV) *m/z* 352, 350, 348 ($M^{+\cdot}$, 0.3, 0.5, 0.3), 337, 335, 333 [$(M-H_3C\cdot)^+$, 6, 8, 6], 292 {$[M-(CH_3)_2CO]^{+\cdot}$, 76}, 274 (73), 210 (99), 182 (47), 103 (100).

Elemental Analysis Found: C, 37.82; H, 2.95; Br, 45.78; N, 3.81; $C_{11}H_{11}Br_2NO_2$ requires: C, 37.85; H, 3.18; Br, 45.79; N, 4.01%.

Optical Rotation $[\alpha]_D^{20}$ -1.07 ° (*c* 3.1, $CHCl_3$).

Concentration of fraction C (R_f 0.6) yielded a white solid. Recrystallization (hexane/EtOAc) of this material then gave compound **78** (1.52 g, 7%) as colourless prisms, m.p. 180-181 °C.

^{1}H NMR (300 MHz) δ: 6.14-6.09 (2H, m), 4.82 (1H, d, *J* = 6.4 Hz), 4.66-4.65 (1H, m), 2.85 (1H, d, *J* = 4.6 Hz), 1.50 (3H, s), 1.37 (3H, s).

^{13}C NMR (75.4 MHz) δ: 127.8 (CH), 123.1 (CH), 119.8 (C), 108.0 (C), 71.9 (CH), 68.5 (CH), 38.5 (CH), 31.2 (C), 29.7 (C), 24.7 (CH_3), 23.2 (CH_3).

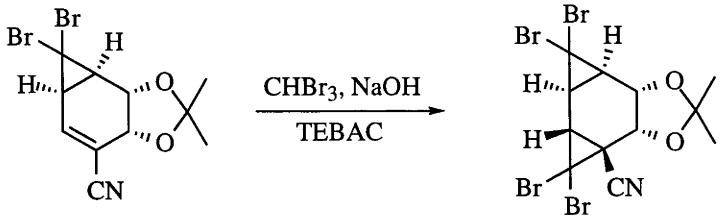
IR ν_{max} 2990, 2936, 2242, 1383, 1374, 1217, 1061 cm^{-1}.

EIMS (70eV) *m/z* 337, 335, 333 [$(M-H_3C\cdot)^+$, 20, 25, 20], 292 {$[M-(CH_3)_2CO]^{+\cdot}$, 36}, 210 (39), 182 (38), 103 (62).

Elemental Analysis Found: C, 37.67; H, 2.89; Br, 45.52; N, 3.92; $C_{11}H_{11}Br_2NO_2$ requires: C, 37.85; H, 3.18; Br, 45.79; N, 4.01%.

Optical Rotation $[\alpha]_D^{20}$ -36.3 ° (*c* 3.6, $CHCl_3$).

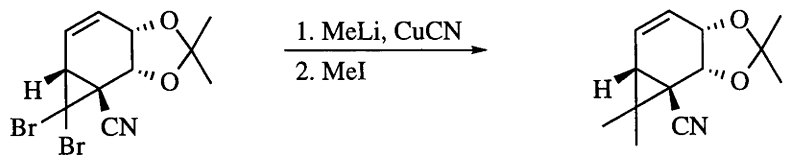
(3a*R*,3b*S*,4a*R*,4b*R*,5a*R*,5b*S*)-4,4,5,5-Tetrabromohexahydro-2,2-dimethyldicyclopropa[*e*,*g*]-1,3-benzodioxolo-3b(3a*H*)-carbonitrile (75).



76 **75**

Sodium hydroxide (370 μL of a 50% w/w aqueous solution, 0.47 mmol) was added, dropwise, to a magnetically stirred solution of compound **76** (102 mg, 0.30 mmol), bromoform (333 μL, 3.82 mmol) and benzyltriethylammonium chloride (5 mg, 0.02 mmol) in dry benzene (3 mL) maintained at 5 °C (ice-bath). The dark-coloured reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (10 mL) and water (5 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), compound **75** (145 mg, 98%) as a white solid, m.p. 219-220 °C. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **75** produced under the conditions defined earlier (see page 115).

(3a*S*,5a*S*,6a*S*,6b*R*)-2,2,6,6-Tetramethyl-3a,6,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (65).



78 **65**

Copper cyanide (436 mg, 4.89 mmol) was washed with dry toluene (2 x 2 mL), with the solvent being removed under high vacuum (10^{-3} Torr) after each wash. The tan powder thus obtained was suspended in dry THF (3 mL) under an atmosphere of nitrogen and the resulting suspension was cooled to -78 °C (acetone/dry-ice slush bath) then methyllithium (7.0 mL of a 1.4 M solution in Et_2O, 9.80 mmol) was added dropwise. The heterogeneous mixture produced in this manner was removed from the cold-bath and left to stir at 18 °C for 0.8 h and then recooled to -78 °C. Dibromide **78** (168 mg, 0.489 mmol) was added at -78 °C then the reaction mixture was warmed to 0 °C and allowed to stir at this temperature for 0.1 h. After this time, methyl iodide (1.10 mL, 17.7 mmol) was added slowly over 0.2 h and after an additional 0.2 h the reaction mixture was quenched with ammonium chloride (60 mL of a 10% w/v aqueous solution in 10% ammonia water) then extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) then filtered and concentrated under reduced pressure to an orange oil. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), a white solid. Recrystallization (hexane) of this material then gave compound **65** (83 mg, 78%) as colourless needles, m.p. 93-94 °C.

^{1}H NMR (300 MHz) δ: 5.92 (1H, dd, *J* = 10.4 and 4.2 Hz), 5.83 (1H, dd, *J* = 10.4 and 3.0 Hz), 4.79 (1H, d, *J* = 8.2 Hz), 4.62 (1H, dd, *J* = 10.4 and 3.0 Hz), 1.90 (1H, d, *J* = 4.2 Hz), 1.47 (3H, s), 1.41 (3H, s), 1.32 (3H, s), 1.10 (3H, s).

^{13}C NMR (75.4 MHz) δ: 124.8 (CH), 123.9 (CH), 122.7 (C), 107.3 (C), 72.7 (CH), 69.9 (CH), 34.5 (CH), 34.4 (C), 26.8 (CH_3), 25.0 (CH_3), 24.5 (C), 22.9 (CH_3), 16.9 (CH_3).

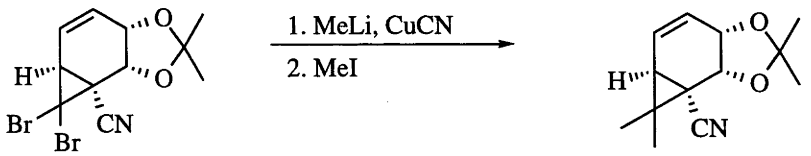
IR ν_{max} 2981, 2940, 2225, 1659, 1458, 1385 cm^{-1}.

EIMS (70eV) *m/z* 219 ($M^{+\cdot}$, 0.4), 204 [$(M\text{-}H_3C\cdot)^+$, 27], 161 {[$M\text{-}(CH_3)_2CO]^{+\cdot}$, 78}, 146 (90), 132 (80), 120 (92), 103 (100).

HRMS Found $(M\text{-}H_3C\cdot)^+$, 204.1029. $C_{13}H_{17}NO_2$ requires $(M\text{-}H_3C\cdot)^+$, 204.1024.

Optical Rotation $[\alpha]_D^{20}$ - 12.3 ° (*c* 2.1, $CHCl_3$).

(3a*S*,5a*R*,6a*R*,6b*R*)-2,2,6,6-Tetramethyl-3a,6,6a,6b-tetrahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (66).



77 **66**

Copper cyanide (444 mg, 4.96 mmol) was washed with dry toluene (2 x 2 mL) with the solvent being removed under high vacuum (10^{-3} Torr) after each wash. The tan powder thus obtained was suspended in dry THF (3 mL) under an atmosphere of nitrogen and the resulting suspension was cooled to -78 °C (acetone/dry-ice slush bath) then methyllithium (7.1 mL of a 1.4 M solution in Et_2O, 9.91 mmol) was added dropwise. The heterogeneous mixture produced in this manner was removed from the cold-bath and left to stir at 18 °C for 0.8 h and then recooled to -78 °C. Dibromide **77** (172 mg, 0.49 mmol) was added at -78 °C then the reaction mixture was warmed to 0 °C and allowed to stir at this temperature for 0.1 h. After this time, methyl iodide (1.1 mL, 17.7 mmol) was added slowly over 0.2 h and after an additional 0.2 h the reaction mixture was quenched with ammonium chloride (60 mL of a 10% w/v aqueous solution in 10% ammonia water) then extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$) then filtered and concentrated under reduced pressure to an orange oil. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate

fractions (R_f0.7), a white solid. Recrystallization (hexane) of this material then gave compound **66** (92 mg, 85%) as colourless needles, m.p. 77-78 °C.

^{1}H NMR (300 MHz) δ: 5.91 (1H, dd, *J* = 10.4 and 5.4 Hz), 5.70 (1H, dd, *J* = 10.4 and 2.8 Hz), 4.48 (1H, d, *J* = 6.9 Hz), 4.30 (1H, m), 1.84 (1H, d, *J* = 5.4), 1.47 (6H, s), 1.39 (3H, s), 0.92 (3H, s).

^{13}C NMR (75.4 MHz) δ: 125.6 (CH), 123.7 (CH), 120.6 (C), 110.4 (C), 71.0 (CH), 68.8 (CH), 30.4 (CH), 29.0 (C), 27.8 (CH_3), 26.2 (CH_3), 25.8 (CH_3), 21.0 (C), 15.3 (CH_3).

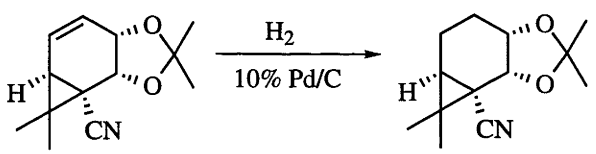
IR ν_{max} 3025, 2984, 2975, 2938, 2230, 1651, 1454, 1243 cm^{-1}.

EIMS (70eV) *m/z* 219 ($M^{+\cdot}$, 1.2), 204 [$(M-H_3C\cdot)^+$, 25], 161 {[$M-(CH_3)_2CO]^{+\cdot}$, 100}, 146 (57), 132 (45), 120 (92).

- **HRMS** Found $(M-H_3C\cdot)^+$, 204.1025. $C_{13}H_{17}NO_2$ requires $(M-H_3C\cdot)^+$, 204.1024.

Optical Rotation $[\alpha]_D^{20}$ + 10.1 ° (*c* 1.6, $CHCl_3$).

(3a*S*,5a*R*,6a*R*,6b*R*)-2,2,6,6-Tetramethylhexahydrocyclopropa[*e*]-1,3-benzodioxolo-6a(5a*H*)-carbonitrile (81).



66 **81**

10% Palladium on carbon (570 mg) was added to a solution of compound **66** (717 mg, 3.27 mmol) in absolute EtOH (40 mL) and the resulting mixture was stirred under an atmosphere of dihydrogen at 18 °C for 40 h. The mixture thus obtained was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f0.8), compound **81** (719 mg, 99%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.14 (1H, d, *J* = 5.7 Hz), 3.89-3.87 (1H, m), 2.12-2.09 (1H, m), 1.68-1.66 (1H, m), 1.30-1.19 (3H, m), 1.55 (3H, s), 1.39 (3H, s), 1.37 (3H, s), 1.03 (3H, s).

^{13}C NMR (75.4 MHz) δ: 121.2 (C), 109.0 (C), 75.2 (CH), 69.2 (CH), 31.3 (CH or CH_3), 28.2 (CH or CH_3), 26.3 (CH or CH_3), 26.2 (CH or CH_3), 26.1 (CH_2), 25.7 (C), 21.1 (C), 16.9 (CH_2), 16.3 (CH or CH_3).

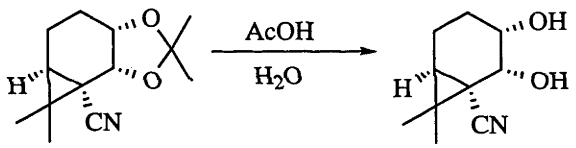
IR ν_{max} 2986, 2938, 2230, 1454, 1381, 1248 cm^{-1}.

EIMS (70eV) *m/z* 206 [$(M\text{-}H_3C\cdot)^+$, 27], 163{[$M\text{-}(CH_3)_2CO]^{+\cdot}$, 21}, 146 (63), 104 (100).

HRMS Found $(M\text{-}H_3C\cdot)^+$, 206.1186. $C_{13}H_{19}NO_2$ requires $(M\text{-}H_3C\cdot)^+$, 206.1181.

Optical Rotation $[\alpha]_D^{20}$ - 1.9 ° (*c* 1.9, $CHCl_3$).

(1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-7,7-dimethylbicyclo[4.1.0]heptane-1-carbonitrile (82).



81 **82**

A magnetically stirred solution of compound **81** (703 mg, 3.18 mmol) in acetic acid (80 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was then diluted with water (10 mL) and EtOAc (200 mL). The separated aqueous phase was extracted with EtOAc (3 x 50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 hexane/EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.1), compound **82** (547 mg, 94%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 3.89 (1H, m), 3.67 (1H, bs), 3.54-3.52 (1H, m), 2.99 (1H, bs), 2.08-2.03 (1H, m), 1.88-1.77 (1H, m), 1.46-1.44 (1H, m), 1.43 (1H, d, J = 7.1 Hz), 1.38 (3H, s), 1.30-1.24 (1H, m), 1.07 (3H, s).

^{13}C NMR (75.4 MHz) δ: 122.2 (C), 67.6 (CH), 65.4 (CH), 30.4 (CH), 27.0 (CH_2), 26.7 (CH_3), 26.0 (C), 21.2 (C), 15.8 (CH_3), 13.9 (CH_2).

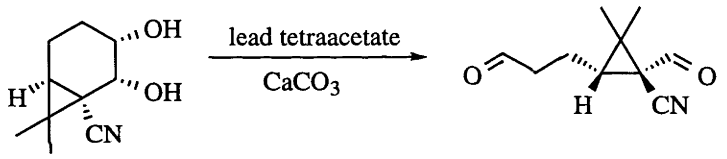
IR ν_{max} 3325 (br), 2919, 2225, 1456, 1119, 1072 cm^{-1}.

EIMS (70eV) *m/z* 182 [(MH^+), 1], 163 [$(M-H_2O)^{+\cdot}$, 30], 137 (87), 122 (76), 108 (100), 94 (70).

HRMS Found $(M-H_2O)^{+\cdot}$, 163.0996. $C_{10}H_{13}NO$ requires $(M-H_2O)^{+\cdot}$, 163.0997.

Optical Rotation $[\alpha]_D^{20}$ + 1.0 ° (*c* 1.6, H_2O).

(1*R*,3*R*)-1-Formyl-2,2-dimethyl-3-(3-oxopropyl)cyclopropane-carbonitrile (83).



82 **83**

A solution of lead tetraacetate (169 mg, 0.38 mmol) in dry CH_2Cl_2 (3 mL) was added, dropwise, to a magnetically stirred suspension of compound **82** (33 mg, 0.18 mmol) and calcium carbonate (216 mg, 2.16 mmol) in dry CH_2Cl_2 (6 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.75 h the reaction mixture was quenched with Et_2O (20 mL) and the resulting mixture filtered through a short pad of TLC-grade silica gel. The filtrate was then concentrated under reduced pressure to afford compound **83** (28 mg, 88%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.76 (1H, s), 9.58 (1H, s), 2.55 (2H, apparent t, J = 6.9 Hz), 2.11-2.06 (3H, m), 1.50 (3H, s), 1.38 (3H, s).

^{13}C NMR (75.4 MHz) δ: 200.7 (CH), 192.9 (CH), 119.1 (C), 46.7 (CH), 44.8 (C), 42.9 (CH_2), 40.5 (C), 26.9 (CH_3), 16.1 (CH_2), 14.7 (CH_3).

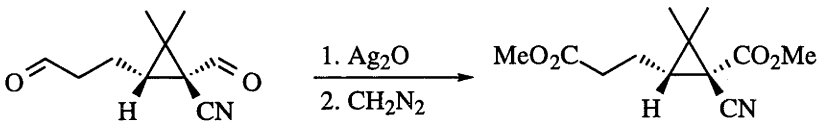
IR ν_{max} 2975, 2919, 2243, 2209, 1731, 1654, 1623, 1387 cm^{-1}.

EIMS (70eV) *m/z* 180 [(MH^+), 20], 179 ($M^{+\cdot}$, 10), 150 (21), 135 (100).

HRMS Found $M^{+\cdot}$, 179.0948 $C_{10}H_{13}NO_2$ requires $M^{+\cdot}$, 179.0946.

Optical Rotation $[\alpha]_D^{20}$ - 20.7 ° (*c* 2.8, $CHCl_3$).

Methyl (1*R*,2*R*)-2'-Cyano-2'-methoxycarbonyl-3',3'-dimethyl-3-cyclopropylpropanoate (85).



83 **85**

Potassium hydroxide (6.5 mL of a 1.05 M solution in H_2O, 6.95 mmol) was added, dropwise, to a magnetically stirred solution of silver nitrate (143 mg, 0.85 mmol) and compound **83** (39 mg, 0.22 mmol) in water/EtOH (0.8 mL/2 mL). After 6 h at 18 °C the reaction mixture was filtered through a pad of Celite™ and the filtrate acidified to *ca.* pH 2 with 3% HCl then extracted with EtOAc (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the pale-yellow oil thus obtained was dissolved in CH_2Cl_2 (75 mL) and the resulting solution cooled to *ca.* -10 °C (salt-ice bath) and treated with an ethereal solution of diazomethane (excess) until a green colour persisted. After 2 h the reaction mixture was concentrated under reduced pressure and the yellow oil obtained in this way was subjected to flash chromatography (EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), compound **85** (34 mg, 65% from **83**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 3.77 (3H, s), 3.69 (3H, s), 2.35 (2H, apparent dt, *J* = 5.3 and 2.8 Hz), 2.20-2.08 (2H, m), 1.76 (1H, t, *J* = 5.3 Hz), 1.49 (3H, s), 1.31 (3H, s).

^{13}C NMR (75.4 MHz) δ: 177.3 (C), 177.2 (C), 119.1 (C), 53.2 (CH_3), 52.1 (CH_3), 43.2 (CH or CH_3), 35.9 (C), 33.2 (CH_2), 26.7 (CH or CH_3), 22.0 (C), 18.9 (CH_2), 14.7 (CH or CH_3).

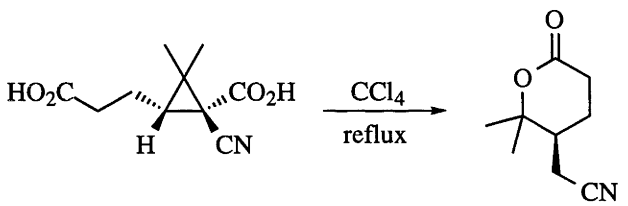
IR ν_{max} 2956, 2931, 2237, 1739, 1438, 1294, 1267 cm^{-1}.

EIMS (70eV) *m/z* 240 [(MH^+), 6], 224 [$(M\text{-}H_3C\cdot)^+$, 20], 207 (65), 175 (80), 148 (100).

HRMS Found $(M\text{-}H_3C\cdot)^+$, 224.0923. $C_{12}H_{17}NO_4$ requires $(M\text{-}H_3C\cdot)^+$, 224.0922.

Optical Rotation $[\alpha]_D^{20}$ - 15.0 ° (*c* 1.4, $CHCl_3$).

(5*S*)-5-Cyanomethyl-6,6-dimethyl-2H-pyran-2-one (86).



84 **86**

A solution of compound **84** (41 mg, 0.19 mmol) in CCl_4 was heated at reflux for 6 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue subjected to flash chromatography (EtOAc elution). Concentration of the appropriate fractions (R_f 0.7) then gave compound **86** (18 mg, 56%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 2.61-2.56 (3H, m), 2.32-2.14 (3H, m), 1.98-1.90 (1H, m), 1.48 (3H, s), 1.34 (3H, s).

^{13}C NMR (75.4 MHz) δ: 170.2 (C), 118.2 (C), 83.7 (C), 39.7 (CH), 29.3 (CH_3), 28.8 (CH_2), 23.4 (CH_3), 22.7 (CH_2), 19.7 (CH_2).

IR ν_{max} 2983, 2930, 2940, 2248, 1731, 1277 cm^{-1}.

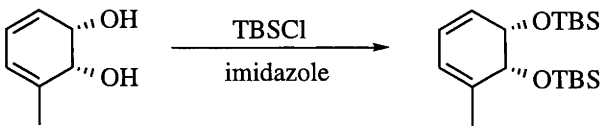
EIMS (70eV) *m/z* 167 ($M^{+\cdot}$, 16), 152 [$(M\text{-}H_3C\cdot)^+$, 33], 124 (48), 109 (44), 81 (95).

HRMS Found $M^{+\cdot}$, 167.0945. $C_9H_{13}NO_2$ requires $M^{+\cdot}$, 167.0946.

Optical Rotation $[\alpha]_D^{20}$ - 12.3 ° (*c* 1.3, $CHCl_3$).

6.3 Experimental Details Associated with Work Described in Chapter Three

(1*S*,2*R*)-[(3-Methyl-3,5-cyclohexadiene-1,2-diyl)*bis*(oxy)]*bis*(1,1-dimethylethyl)dimethylsilane (101).



17 **101**

A solution of *tert*-butyldimethylsilyl chloride (2.63 g, 17.5 mmol) in dry DMF (5 mL) was added, dropwise, to a magnetically stirred solution of (1*S*,2*R*)-*cis*-3-methyl-3,5-cyclohexadiene-1,2-diol (**17**) (880 mg, 7.0 mmol) and imidazole (1.90 g, 28.0 mmol) in dry DMF (10 mL) maintained at 18 °C under a nitrogen atmosphere. After stirring for 3 h the reaction mixture was diluted with water (70 mL) and Et_2O (100 mL). The separated aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (7:3 Et_2O/CH_2Cl_2 elution) which afforded, after concentration of the appropriate fractions (R_f 0.9), compound **101** (2.44 g, 98%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.84 (1H, dd, *J* = 5.2 and 2.2 Hz), 5.75-5.66 (2H, m), 4.17-4.15 (1H, m), 3.95 (1H, d, *J* = 5.2 Hz), 1.87 (3H, s), 0.91-0.89 (18H, m), 0.10-0.01 (12H, m).

^{13}C NMR (75.4 MHz) δ: 140.1 (C), 128.0 (CH), 124.7 (CH), 119.8 (CH), 73.8 (CH), 71.4 (CH), 26.4 (CH_3), 26.3 (CH_3), 20.8 (CH_3), 18.7 (C), -2.6 (CH_3), -3.7 (CH_3), -3.8 (CH_3), -4.5 (CH_3).

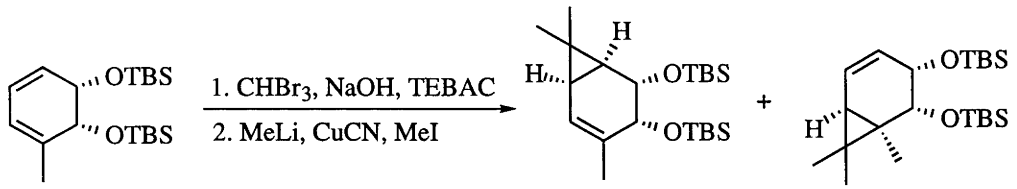
IR ν_{max} 2955, 2930, 1472, 1254, 1098, 837 cm^{-1}.

EIMS (70eV) *m/z* 354 ($M^{+\cdot}$, 28), 339 [$(M-H_3C\cdot)^+$, 4], 239 (17), 165 (27), 147 (64).

HRMS Found $M^{+\cdot}$, 354.2405. $C_{19}H_{38}O_2Si_2$ requires $M^{+\cdot}$, 354.2410.

Optical Rotation $[\alpha]_D^{20}$ + 43.3 ° (*c* 3.2, $CHCl_3$).

(1*R*,2*R*,3*S*,4*R*)-{(4,7,7-Trimethylbicyclo[4.1.0]hept-4-ene-2,3-diyl)*bis*(oxy)}*bis*(1,1-dimethylethyl)dimethylsilane (99) and (1*R*,2*R*,3*S*,6*R*)-{(1,7,7-Trimethylbicyclo[4.1.0]hept-4-ene-2,3-diyl)*bis*(oxy)}*bis*(1,1-dimethylethyl)dimethylsilane (103).



101 **99** **103**

Sodium hydroxide (3.39 mL of a 50% w/w aqueous solution, 42.4 mmol) was added, dropwise, to a magnetically stirred solution of compound **101** (2.4 g, 6.9 mmol), bromoform (3.0 mL, 35.1 mmol) and benzyltriethylammonium chloride (25 mg, 0.10 mmol) in dry benzene (40 mL) maintained at 5 °C (ice-bath). The dark-brown reaction mixture thus obtained was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (150 mL) and water (100 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.6), a *ca.* 2:1 mixture (as judged by ^1H NMR analysis) of compounds **100** and **102** (2.44 g, 68%) as a clear, colourless oil. All attempts to separate the components of this mixture failed, and as such, this material was used, without purification, in the next step of the reaction sequence.

Copper cyanide (4.2 g, 47 mmol) was washed with dry toluene (2 x 5 mL) with the solvent being removed under high vacuum (10^{-3} Torr) after each wash. The tan powder thus obtained was suspended in dry THF (50 mL) under an atmosphere of nitrogen and the resulting suspension was cooled to -78 °C (acetone/dry-ice slush bath) then methyllithium (67.0 mL of a 1.4 M solution in Et_2O, 93.0 mmol) was added dropwise. The heterogeneous mixture produced in this manner was removed from the cold-bath and left to stir at 18 °C for 0.8 h and then recooled to -78 °C. A *ca.* 2:1 mixture of

compounds **100** and **102** (2.44 g, 4.64 mmol) in dry THF (5 mL) was added then the reaction mixture was warmed to 0 °C and allowed to stir at this temperature for 0.1 h. After this time, methyl iodide (5.5 mL, 94 mmol) was added slowly over 0.2 h and after an additional 0.2 h the reaction mixture was quenched with ammonium chloride (200 mL of a 10% w/v aqueous solution in 10% ammonia water) then extracted with Et_2O (2 x 100 mL). The separated aqueous phase was extracted with Et_2O (3 x 150 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (hexane elution) which afforded two fractions, A and B.

Concentration of fraction A (R_f0.8) yielded compound **103** (1.0 g, 53%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.87-5.82 (1H, m), 5.72 (1H, dd, *J* = 8.3 and 2.6 Hz), 3.82 (1H, dd, *J* = 6.1 and 2.6 Hz), 3.52 (1H, d, *J* = 2.6 Hz), 1.55 (1H, s), 1.23 (3H, s), 1.16 (3H, s), 0.96 (3H, s), 0.91 (9H, s), 0.88 (9H, s), 0.06-0.02 (12H, m).

^{13}C NMR (75.4 MHz) δ: 131.9 (CH), 130.4 (CH), 70.5 (CH), 69.0 (CH), 32.9 (CH or CH_3), 27.5 (C), 26.3 (CH or CH_3), 26.2 (CH_3), 23.1 (CH), 18.7 (C), 17.8 (CH_3), 17.5 (CH_3), -3.8 (CH_3), -4.5 (CH_3), -4.6 (CH_3).

IR ν_{max} 2956, 2929, 2858, 1473, 1253, 1119, 836 cm^{-1}.

EIMS (70eV) *m/z* 396 ($M^{+\cdot}$, 13), 381 [$(M\text{-}H_3C\cdot)^+$, 30], 339 [$(M\text{-}H_9C_4\cdot)^+$, 33], 265 (34), 147 (53).

HRMS Found $M^{+\cdot}$, 396.2886. $C_{22}H_{44}O_2Si_2$ requires $M^{+\cdot}$, 396.2879.

Optical Rotation $[\alpha]_D^{20}$ + 103.7 ° (*c* 3.0, $CHCl_3$).

Concentration of fraction B (R_f0.7) yielded compound **99** (500 mg, 27%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.39 (1H, bs), 3.66 (1H, d, *J* = 2.6 Hz), 3.33 (1H, dd, *J* = 5.0 and 2.6 Hz), 1.73 (3H, s), 1.55 (1H, s), 1.15-1.13 (1H, m), 1.12 (3H, s), 0.93 (3H, s), 0.91 (9H, s), 0.87 (9H, s), 0.14-0.05 (12H, m).

^{13}C NMR (75.4 MHz) δ: 140.1 (C), 123.1 (CH), 73.3 (CH), 70.3 (CH), 27.8 (CH or CH_3), 27.5 (CH or CH_3), 26.5 (CH_3), 26.3 (CH or CH_3), 25.6 (CH or CH_3), 24.2 (C), 22.0 (CH or CH_3), 18.4 (C), 15.4 (CH or CH_3), -3.8 (CH_3), -4.2 (CH_3).

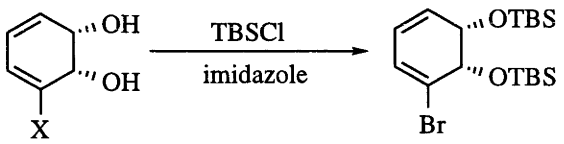
IR ν_{max} 2956, 2929, 2886, 2857, 1472, 835 cm^{-1}.

EIMS (70eV) *m/z* 396 ($M^{+\cdot}$, 100), 381 [$(M-H_3C\cdot)^+$, 80], 339 [$(M-H_9C_4\cdot)^+$, 46], 265 (48), 147 (60).

HRMS Found $M^{+\cdot}$, 396.2878. $C_{22}H_{44}O_2Si_2$ requires $M^{+\cdot}$, 396.2879.

Optical Rotation $[\alpha]_D^{20}$ - 103.3 ° (*c* 2.1, $CHCl_3$).

(1*S*,2*S*)-[(3-Bromo-3,5-cyclohexadiene-1,2-diyl)*bis*(oxy)]*bis*(1,1-dimethylethyl)dimethylsilane (104).



14 (X=Br) **104**

A solution of *tert*-butyldimethylsilyl chloride (23.0 g, 150 mmol) in dry DMF (50 mL) was added, dropwise, to a magnetically stirred solution of (1*S*,2*S*)-*cis*-3-bromo-3,5-cyclohexadiene-1,2-diol (**14**, X=Br) (7.5 g, 39.5 mmol) and imidazole (16.3 g, 240 mmol) in dry DMF (120 mL) maintained at 18 °C under a nitrogen atmosphere. After stirring for 3 h the reaction mixture was diluted with water (200 mL) and Et_2O (150 mL). The separated aqueous phase was extracted with Et_2O (2 x 200 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (7:3 Et_2O/CH_2Cl_2 elution) which afforded, after concentration of the appropriate fractions (R_f0.9) compound **104** (15.6 g, 94%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.31 (1H, d, *J* = 5.6 Hz), 5.86-5.82 (1H, m), 5.77-5.72 (1H, m), 4.50-4.47 (1H, m), 4.01 (1H, d, *J* = 5.6 Hz), 0.93 (9H, s), 0.89 (9H, s), 0.14-0.01 (12H, m).

^{13}C NMR (75.4 MHz) δ: 133.3 (CH), 127.4 (CH), 123.7 (C), 122.6 (CH), 72.9 (CH), 70.9 (CH), 23.7 (CH_3), 23.6 (CH_3), 16.1 (C), -6.8 (CH_3), -7.0 (CH_3).

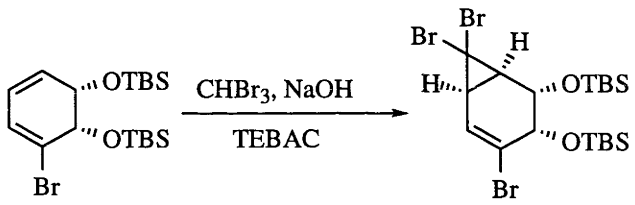
IR ν_{max} 2995, 2930, 2858, 1472, 1390 cm^{-1}.

EIMS (70eV) *m/z* 420, 418 ($M^{+\cdot}$, 100, 94), 339 [$(M\text{-}Br\cdot)^+$, 37], 147 (100), 73 (64).

HRMS Found $M^{+\cdot}$, 420.1361. $C_{18}H_{35}{}^{81}BrO_2$ requires $M^{+\cdot}$, 420.1338. Found $M^{+\cdot}$, 418.1376. $C_{18}H_{35}{}^{79}BrO_2$ requires $M^{+\cdot}$, 418.1358.

Optical Rotation $[\alpha]_D{}^{20}$ + 30.5 ° (*c* 4.2, $CHCl_3$).

(1*R*,2*R*,3*S*,4*R*)-{(4,7,7-Tribromobicyclo[4.1.0]hept-4-ene-2,3-diyl)*bis*(oxy)}*bis*(1,1-dimethylethyl)dimethylsilane (105).



104 **105**

Sodium hydroxide (6.70 mL of a 50% w/w aqueous solution, 83.8 mmol) was added, dropwise, to a magnetically stirred solution of compound **104** (5.8 g, 13.8 mmol), bromoform (6.1 mL, 69.6 mmol) and benzyltriethylammonium chloride (45 mg, 0.20 mmol) in dry benzene (50 mL) maintained at 5 °C (ice-bath). The dark-brown reaction mixture thus obtained was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (600 mL) and water (300 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 400 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (hexane elution) which yielded, after concentration of the appropriate fractions (R_f 0.6), compound **105** (5.20 g, 64%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.09 (1H, d, *J* = 3.6 Hz), 4.09 (1H, d, *J* = 3.6 Hz), 3.69 (1H, dd, *J* = 6.1 and 2.8 Hz), 2.35 (1H, dd, *J* = 10.4 and 2.8 Hz), 1.99 (1H, dd, *J* = 10.4 and 6.1 Hz), 0.95 (9H, s), 0.90 (9H, s), 0.21-0.13 (12H, m).

^{13}C NMR (75.4 MHz) δ: 129.2 (C), 127.1 (CH), 76.4 (CH), 73.4 (CH), 38.3 (C), 34.0 (CH), 33.1 (CH), 26.3 (CH_3), 26.2 (CH_3), 18.5 (C), -4.2 (CH_3).

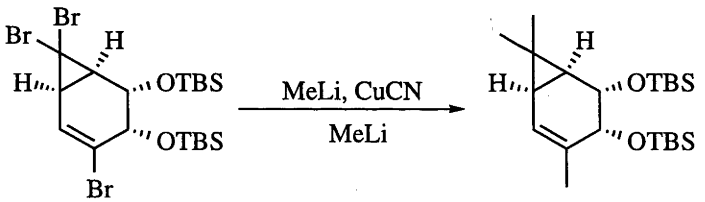
IR ν_{max} 2955, 2929, 2895, 2857, 1625, 1388 cm^{-1}.

EIMS (70eV) *m/z* 593, 591, 589, 587 ($M^{+\cdot}$, 0.2, 0.18, 0.16, 0.04), 536, 534, 532, 530 [$(M-H_9C_4\cdot)^+$, 10, 8, 7, 4], 511 (21), 452 (20), 172 (29), 147 (100).

HRMS Found $(M-H_9C_4\cdot)^+$, 536.8982. $C_{19}H_{35}{}^{81}Br_3O_2Si_2$ requires $(M-H_9C_4\cdot)^+$, 536.8960. Found $(M-H_9C_4\cdot)^+$, 534.8992. $C_{19}H_{35}{}^{79}Br^{81}Br_2O_2Si_2$ requires $(M-H_9C_4\cdot)^+$, 534.8980. Found $(M-H_9C_4\cdot)^+$, 532.9011. $C_{19}H_{35}{}^{79}Br_2{}^{81}BrO_2Si_2$ requires $(M-H_9C_4\cdot)^+$, 532.9000. Found $(M-H_9C_4\cdot)^+$, 530.9038. $C_{19}H_{35}{}^{79}Br_3O_2Si_2$ requires $(M-H_9C_4\cdot)^+$, 530.9021.

Optical Rotation $[\alpha]_D{}^{20}$ - 64.2 ° (*c* 3.8, $CHCl_3$).

(1*R*,2*R*,3*S*,4*R*)-{(4,7,7-Trimethylbicyclo[4.1.0]hept-4-ene-2,3-diyl)*bis*(oxy)}*bis*(1,1-dimethylethyl)dimethylsilane (99).

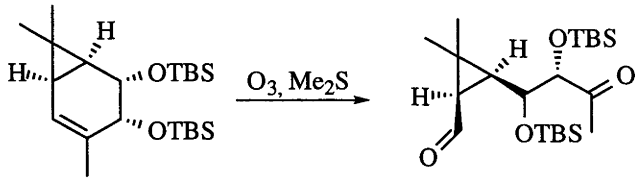


105 **99**

Copper cyanide (17.1 g, 190 mmol) was washed with dry toluene (2 x 5 mL) with the solvent being removed under high vacuum (10^{-3} Torr) after each wash. The tan powder thus obtained was suspended in dry THF (150 mL) under an atmosphere of nitrogen and the resulting suspension was cooled to -78 °C (acetone/dry-ice slush bath) then methyllithium (273 mL of a 1.4 M solution in Et_2O, 380 mmol) was added dropwise. The heterogeneous mixture produced in this manner was removed from the

cold-bath and left to stir at ambient temperature for 0.8 h and then recooled to -78 °C. Compound **105** (4.88 g, 8.30 mmol) in dry THF (10 mL) was added then the reaction mixture was warmed to 0 °C and allowed to stir at this temperature for 0.1 h. After this time, methyl iodide (134 mL, 186 mmol) was added slowly over 0.2 h and after an additional 0.2 h the reaction mixture was quenched with ammonium chloride (400 mL of a 10% w/v aqueous solution in 10% ammonia water) then extracted with Et_2O (2 x 100 mL). The separated aqueous phase was extracted with Et_2O (3 x 400 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.7) compound **99** (2.30 g, 70%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **99** produced under the conditions defined earlier (see page 127).

(1*R*,3*S*,4*S*,5*R*)-3-{1,2-*Bis*[(1,1-dimethylethyl)dimethylsilyl]oxy-3-oxobutyl}-2,2-dimethylcyclopropanecarboxaldehyde (106).



99 **106**

A stream of ozone (*ca.* 40% ozone in oxygen) was passed through a magnetically stirred solution of compound **99** (681 mg, 1.72 mmol) in dry CH_2Cl_2 (40 mL) maintained at -78 °C (acetone/dry-ice slush bath) until the solution turned blue (*ca.* 0.2 h). The excess ozone was displaced by a stream of oxygen and dimethyl sulfide (2.0 mL, 27.2 mmol) was added, dropwise, to the reaction mixture which was then warmed to 18 °C over 4 h, and diluted with water (20 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were then dried

($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (1:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f0.8) compound **106** (574 mg, 78%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.67 (1H, d, *J* = 3.7 Hz), 4.20 (1H, dd, *J* = 12.0 and 3.2 Hz), 3.75 (1H, d, *J* = 3.2 Hz), 2.20 (3H, s), 1.97 (1H, dd, *J* = 12.0 and 2.3 Hz), 1.53 (1H, t, *J* = 9.2 Hz), 1.26 (3H, s), 1.25 (3H, s), 0.93 (9H, s), 0.88 (9H, s), 0.20 (3H, s), 0.12 (6H, s), 0.04 (3H, s).

^{13}C NMR (75.4 MHz) δ: 212.7 (C), 201.0 (CH), 82.5 (CH), 72.9 (CH), 40.3 (CH or CH_3), 39.4 (CH or CH_3), 31.1 (C), 29.1 (CH or CH_3), 28.5 (CH or CH_3), 26.2 (CH_3), 26.1 (CH_3), 18.6 (C), 15.3 (CH or CH_3), -3.0 (CH_3), -4.3 (CH_3), -4.9 (CH_3).

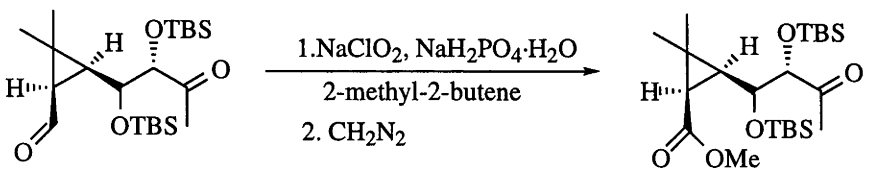
IR ν_{max} 2930, 2958, 2858, 1703, 1472, 1254, 1118 cm^{-1}.

EIMS (70eV) *m/z* 428 ($M^{+\cdot}$, 0.7), 413 [$(M-H_3C\cdot)^+$, 0.3], 385 (4), 302 (30), 241 (66).

HRMS Found $M^{+\cdot}$, 428.2788. $C_{22}H_{44}O_4Si_2$ requires $M^{+\cdot}$, 428.2778.

Optical Rotation $[\alpha]_D^{20}$ - 25.4 ° (*c* 3.8, $CHCl_3$).

Methyl (1*R*,3*S*,4*S*,5*R*)-3-{1,2-*Bis*[(1,1-dimethylethyl)dimethylsilyl]oxy-3-oxobutyl}-2,2-dimethylcyclopropanecarboxylate (107).



106 **107**

A magnetically stirred solution of compound **106** (722 mg, 1.69 mmol) in *tert*-butanol (9.6 mL) and water (2.4 mL) was treated with 2-methyl-2-butene (2.1 mL of a 2M solution in THF, 4.2 mmol) followed by sodium dihydrogen orthophosphate monohydrate (245 mg, 1.77 mmol) at 18 °C. After 0.2 h sodium chlorite (457 mg, 5.1

mmol) was added in one portion and stirring then continued at 0 °C (ice-bath) for 3 h. The reaction mixture was then quenched with HCl (30 mL of a 1M aqueous solution) and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colourless oil. This material (crude carboxylic acid) was dissolved in CH_2Cl_2 (75 mL), cooled to *ca.* -10 °C (salt-ice bath) then treated with an ethereal solution of diazomethane (excess) until a green colour persisted. After 2 h the reaction mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (1:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), compound **107** (664 mg, 86% from **106**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.22 (1H, d, J = 9.8 Hz), 3.78 (1H, s), 3.62 (3H, s), 2.21 (3H, s), 1.61 (1H, d, J = 8.0 Hz), 1.25-1.22 (1H, m), 1.25 (3H, s), 1.17 (3H, s), 0.93 (9H, s), 0.88 (9H, s), 0.20 (3H, s), 0.12 (3H, s), 0.10 (3H, s), 0.03 (3H, s).

^{13}C NMR (75.4 MHz) δ: 213.2 (C), 172.8 (C), 82.8 (CH), 78.0 (CH), 51.9 (CH_3), 36.2 (CH or CH_3), 29.9 (CH or CH_3), 29.2 (CH or CH_3), 28.9 (CH or CH_3), 26.3 (CH_3), 18.6 (C), 15.0 (CH or CH_3), -2.7 (CH_3), -4.0 (CH_3), -4.6 (CH_3).

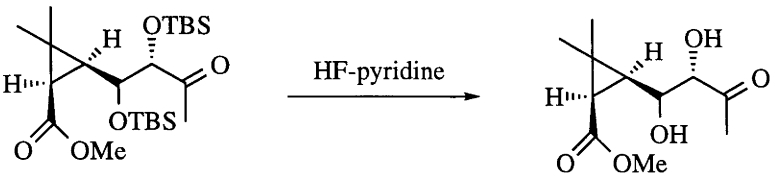
IR ν_{max} 2955, 2930, 2858, 1726, 1472, 1254, 1083 cm^{-1}.

EIMS (70eV) *m/z* 458 ($M^{+\cdot}$, 2), 302 (30), 271 (100), 245 (72), 211 (25).

HRMS Found $M^{+\cdot}$, 458.2875. $C_{23}H_{46}O_5Si_2$ requires $M^{+\cdot}$, 458.2883.

Optical Rotation $[\alpha]_D^{20}$ - 20.7 ° (*c* 2.3, $CHCl_3$).

Methyl (1*R*,3*S*,4*S*,5*R*)-3-(1,2-Dihydroxy-3-oxobutyl)-2,2-dimethyl-cyclopropanecarboxylate (98).



107 **98**

Hydrogen fluoride-pyridine (0.5 mL) was added, dropwise, to a magnetically stirred solution of compound **107** (103 mg, 0.23 mmol) in dry acetonitrile (1.5 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (EtOAc elution) which afforded, after concentration of the appropriate fractions (R_f 0.7), compound **98** (32 mg, 62%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.48 (1H, dd, *J* = 9.9 and 4.0 Hz), 4.29 (1H, d, *J* = 4.0 Hz), 3.64 (3H, s), 2.46 (1H, bs), 2.26 (3H, s), 1.66 (1H, bs), 1.57 (1H, d, *J* = 8.7 Hz), 1.36 (1H, d, *J* = 9.9 Hz), 1.33 (3H, s), 1.22 (3H, s).

^{13}C NMR (75.4 MHz) δ: 209.2 (C), 172.8 (C), 80.6 (CH), 68.9 (CH), 52.0 (CH_3), 33.3 (CH or CH_3), 30.3 (CH or CH_3), 29.2 (CH or CH_3), 27.6 (CH or CH_3), 25.5 (C), 15.1 (CH or CH_3).

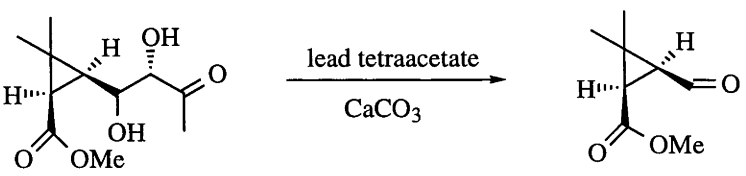
IR ν_{max} 3386 (b), 2954, 2928, 1724, 1440, 1378, 1197, 1179 cm^{-1}.

EIMS (70eV) *m/z* 231 [(MH^+), 2)], 230 ($M^{+\cdot}$, 0.6), 215 [($M-H_3C\cdot)^+$, 2], 198 (3), 187 [($M-C_2H_3O\cdot)^+$, 35], 155 (47), 125 (100).

HRMS Found $M^{+\cdot}$, 230.1154. $C_{11}H_{18}O_5$ requires $M^{+\cdot}$, 230.1154.

Optical Rotation $[\alpha]_D^{20}$ + 29.7 ° (*c* 1.9, $CHCl_3$).

Methyl (1*R*,3*S*)-3-Formyl-2,2-dimethylcyclopropanecarboxylate (87).



98 **87**

A solution of lead tetraacetate (104 mg, 0.235 mmol) in dry CH_2Cl_2 (2 mL) was added, dropwise, to a magnetically stirred suspension of compound **98** (25 mg, 0.11 mmol) and calcium carbonate (133 mg, 1.33 mmol) in dry CH_2Cl_2 (2 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.75 h the reaction mixture was quenched with Et_2O (20 mL) then filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (1:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.6), compound **87** (12 mg, 71%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.76 (1H, d, *J* = 6.5 Hz), 3.71 (3H, s), 2.14 (1H, d, *J* = 8.0 Hz), 1.85-1.84 (1H, t, *J* = 8.0 Hz), 1.55 (3H, s), 1.27 (3H, s).

^{13}C NMR (75.4 MHz) δ: 200.8 (CH), 170.7 (C), 57.5 (CH_3), 41.1 (CH), 36.3 (CH), 30.2 (C), 28.5 (CH_3), 15.2 (CH_3).

IR ν_{max} 2957, 2890, 1729, 1701, 1440, 1202, 1136 cm^{-1}.

EIMS (70eV) *m/z* 157 [(MH^+), 20)], 141 [($M-H_3C\cdot)^+$, 35)], 128 [($M-CO)^{+\cdot}$, 60)], 114 (32), 97 [($M-CH_3CO_2\cdot)^+$, 100)].

HRMS Found ($M-H_3C\cdot)^+$, 141.0553. $C_8H_{12}O_3$ requires ($M-H_3C\cdot)^+$, 141.0551.

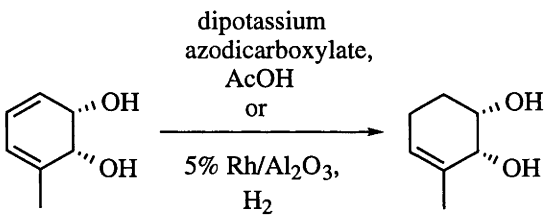
Optical Rotation $[\alpha]_D^{20}$ - 55.0 ° (*c* 1.3, $CHCl_3$).

7.4 Experimental Details Associated with Work Described in Chapter Four

General Procedure for the Extraction of (1*S*,2*R*)-*cis*-3-methyl-3,5-cyclohexadiene-1,2-diol (17) from the Fermentation Broth Supplied by Genencor International Inc.

The fermentation broth containing compound **17** was stored in 250 mL plastic bottles at -30 °C. Prior to extraction the broth (247 g) was thawed out away from direct light. The resulting material was poured into a separating funnel and diluted with EtOAc (500 mL) and brine (200 mL). The separated aqueous layer was extracted with EtOAc (4 x 500 mL) and the combined organic phases were then washed with water (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a tan solid (34 g) which was comprised, for the most part, of the title compound **17**. This material was used, without purification, in the next step of the reaction sequence.

(1*S*,2*R*)-3-Methylcyclohex-3-ene-1,2-diol (133).



17 **133**

Method One:

Acetic acid (4.2 mL, 73.3 mmol) was added, dropwise, to a magnetically stirred solution of dipotassium azodicarboxylate (6.9 g, 36 mmol) and (1*S*,2*R*)-*cis*-3-methyl-3,5-cyclohexadiene-1,2-diol (**17**) (567 mg, 4.49 mmol) in MeOH (20 mL) maintained at 0 °C (ice-bath). After nitrogen evolution had ceased (*ca.* 0.75 h), the solvent was removed under reduced pressure and the residue treated with EtOAc (200 mL) and

water (100 mL). The separated organic phase was washed with $NaHCO_3$ (100 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography (Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.4), a white solid. Recrystallization (Et_2O) of this material then gave compound **133** (475 mg, 83%) as colourless needles, m.p. 73-74 °C (lit.[138] m.p. 82-83 °C).

^{1}H NMR (300 MHz) δ: 5.54 (1H, m), 3.91 (1H, d, J = 3.8 Hz), 3.76-3.70 (1H, m), 2.76 (2H, bs), 2.11-2.02 (2H, m), 1.79 (3H, bs), 1.79-1.63 (2H, m).

^{13}C NMR (75.4 MHz) δ: 133.8 (C), 125.8 (CH), 70.4 (CH), 70.0 (CH), 25.6 (CH_2), 24.2 (CH_2), 21.2 (CH_3).

IR ν_{max} 3285 (b), 2940, 2872, 1451, 1128, 1051 cm^{-1}.

EIMS (70eV) *m/z* 128 ($M^{+\cdot}$, 11), 110 [$(M-H_2O)^{+\cdot}$, 15], 84 [$(M-CO_2)^{+\cdot}$, 100], 55 (35).

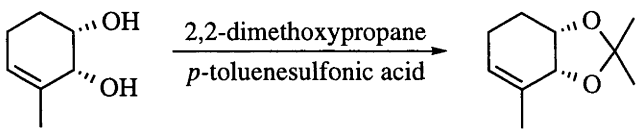
Elemental Analysis Found: C, 65.35; H, 9.52; $C_7H_{12}O_2$ requires: C, 65.60; H, 9.44%.

Optical Rotation $[\alpha]_D^{20}$ - 149.5 ° (*c* 1.9, $CHCl_3$); {lit.[76] $[\alpha]_D^{20}$ - 151.7 ° (*c* 0.6, $CHCl_3$)}.

Method Two:

5% Rhodium on alumina (75 mg) was added to a solution of (1*S*,2*R*)-*cis*-3-methyl-3,5-cyclohexadiene-1,2-diol (**17**) (500 mg, 3.96 mmol) in absolute EtOH (15 mL) and the resulting mixture was stirred under an atmosphere of dihydrogen at 18 °C for 16 h. After this time the reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.4), compound **133** (485 mg, 96%) as a white solid, m.p. 73-74 °C. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **133** prepared by *Method One* (above).

(3a*R*,7a*S*)-2,2,4-Trimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole (128).



133 **128**

p-Toluenesulfonic acid monohydrate (300 mg, 2.3 mmol) was added, in one portion, to a magnetically stirred solution of compound **133** (1.36 g, 10.6 mmol) in 2,2-dimethoxypropane (40 mL, 324 mmol) maintained at *ca.* -10 °C (salt-ice bath) under a nitrogen atmosphere. After 0.5 h the reaction mixture was treated with triethylamine (0.5 mL) then concentrated carefully at atmospheric pressure. The residue thus obtained was partitioned between Et_2O (100 mL) and water (30 mL). The separated aqueous phase was extracted with Et_2O (2 x 50 mL) then the combined organic phases were dried ($MgSO_4$), filtered and concentrated carefully at atmospheric pressure. The material obtained in this way was subjected to flash chromatography (5:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), compound **128** (1.67 g, 96%) as a volatile, clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.59 (1H, bs), 4.27 (2H, s), 2.23-2.08 (2H, m), 1.84-1.68 (2H, m), 1.77 (3H, bs), 1.39 (6H, s).

^{13}C NMR (75.4 MHz) δ: 132.8 (C), 125.9 (CH), 108.8 (C), 75.8 (CH), 74.1 (CH), 28.5 (CH_3), 27.1 (CH_3), 26.1 (CH_2), 21.3 (CH_2), 20.9 (CH_3).

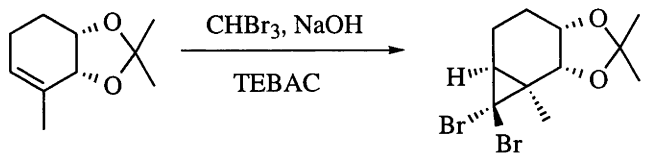
IR ν_{max} 2936, 1368, 1244, 1077 cm^{-1}.

EIMS (70eV) *m/z* 168 ($M^{+\cdot}$, 11), 110 {[M-$(CH_3)_2CO$]$^{+\cdot}$, 15}, 84 (100), 55 (35).

HRMS Found $M^{+\cdot}$, 168.1150. $C_{10}H_{16}O_2$ requires $M^{+\cdot}$, 168.1150.

Optical Rotation $[\alpha]_D^{20}$ + 24.3 ° (*c* 3.0, $CHCl_3$).

(3a*S*,5a*S*,6a*R*,6b*R*)-6,6-Dibromohexahydro-2,2,6a-trimethyl-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (137).



123 **137**

Sodium hydroxide (6.55 mL of a 50% w/w aqueous solution, 75.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **123** (500 mg, 3.0 mmol), bromoform (6.5 mL, 75.5 mmol) and benzyltriethylammonium chloride (20 mg, 0.086 mmol) in dry benzene (10 mL) maintained at 5 °C (ice-bath). The dark-brown reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (200 mL) and water (100 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered, concentrated under reduced pressure with the excess bromoform needing to be removed under high vacuum (10^{-3} Torr). The residue was subjected to flash chromatography (5:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), compound **137** (784 mg, 77%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.17 (1H, d, J = 5.4 Hz), 4.03-4.00 (1H, m), 2.29 (2H, m), 1.68-1.60 (2H, m), 1.51 (3H, s), 1.44 (3H, s), 1.35 (3H, s), 1.34-1.21 (1H, m).

^{13}C NMR (75.4 MHz) δ: 107.7 (C), 75.4 (CH), 73.7 (CH), 46.9 (C), 35.0 (CH_3), 30.4 (C), 28.7 (CH_3), 26.6 (CH_2), 26.3 (CH_3), 23.3 (CH_3), 21.6 (CH_2).

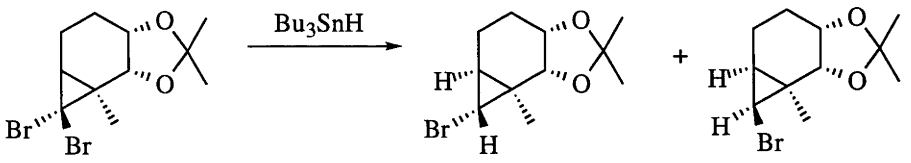
IR ν_{max} 2986, 2935, 1380, 1371 cm^{-1}.

EIMS (70eV) *m/z* 342, 340, 338 ($M^{+\cdot}$, 44, 64, 43), 327, 325, 323 [$(M\text{-}H_3C\cdot)^+$, 46, 66, 45], 284 (100), 283 (54), 259 (64), 201 (100).

HRMS Found $M^{+\cdot}$, 341.9459. $C_{11}H_{16}{}^{81}Br_2O_2$ requires $M^{+\cdot}$, 341.9476. Found $M^{+\cdot}$, 339.9485. $C_{11}H_{16}{}^{79}Br^{81}BrO_2$ requires $M^{+\cdot}$, 339.9496. Found $M^{+\cdot}$, 337.9504. $C_{11}H_{16}{}^{79}Br_2O_2$ requires $M^{+\cdot}$, 337.9517.

Optical Rotation $[\alpha]_D^{20}$ + 7.1 ° (*c* 1.4, $CHCl_3$).

(3a*S*,5a*S*,6*S*,6a*R*,6b*R*)-6-Bromohexahydro-2,2,6a-trimethyl-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (138) and (3a*S*,5a*S*,6*R*,6a*R*,6b*R*)-6-Bromo-2,2,6a-trimethyl-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (139).



137 **138** **139**

Freshly prepared tri-*n*-butyltin hydride (1.2 mL, 4.12 mmol) was added, dropwise, to a magnetically stirred solution of compound **137** (1.17 g, 3.44 mmol) in dry benzene (2 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was stirred at 18 °C for 16 h then concentrated under reduced pressure to provide a *ca.* 2:1 mixture (as determined by ^{1}H NMR analysis) of compounds **138** and **139**. This material was subjected to flash chromatography (2:1 hexane/Et_2O elution) which afforded two fractions, A and B.

Concentration of fraction A (R_f0.5) yielded compound **138** (524 mg, 58%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.24 (1H, d, *J* = 7.2 Hz), 4.14-4.11 (1H, m), 2.84 (1H, d, *J* = 4.0 Hz), 2.01-1.99 (2H, m), 1.76-1.66 (2H, m), 1.47 (3H, s), 1.47-1.36 (1H, m), 1.35 (3H, s), 1.34 (3H, s).

^{13}C NMR (75.4 MHz) δ: 107.4 (C), 75.5 (CH), 74.4 (CH), 36.9 (CH), 28.7 (CH), 26.8 (CH_2), 26.5 (CH_3), 23.3 (CH_3), 22.3 (C), 21.9 (CH_3), 19.5 (CH_2).

IR ν_{max} 2985, 2957, 2933, 1247, 1216 cm^{-1}.

EIMS (70eV) *m/z* 262, 260 ($M^{+\cdot}$, 23, 23), 247, 245 [$(M\text{-}H_3C\cdot)^+$, 92, 91], 181 [$(M\text{-}Br\cdot)^+$, 100], 123 (84), 95 (66).

HRMS Found $M^{+\cdot}$, 262.0395. $C_{11}H_{17}{}^{81}BrO_2$ requires $M^{+\cdot}$, 262.0391. Found $M^{+\cdot}$, 260.0412. $C_{11}H_{17}{}^{79}BrO_2$ requires $M^{+\cdot}$, 260.0411.

Optical Rotation $[\alpha]_D{}^{20}$ + 140.5 ° (*c* 2.1, $CHCl_3$).

Concentration of fraction B (R_f0.3) yielded compound **139** (173 mg, 29%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.09 (1H, d, *J* = 5.5 Hz), 4.03-4.00 (1H, m), 3.04 (1H, d, *J* = 7.7 Hz), 2.17-2.13 (2H, m), 1.66-1.57 (2H, m), 1.46 (3H, s), 1.37-1.29 (1H, m), 1.36 (3H, s), 1.25 (3H, s).

^{13}C NMR (75.4 MHz) δ: 108.3 (C), 74.0 (CH), 72.0 (CH), 29.7 (CH), 28.1 (CH), 27.6 (CH_3), 25.7 (CH_3), 22.9 (C), 21.8 (CH_2), 20.0 (CH_3), 16.5 (CH_3).

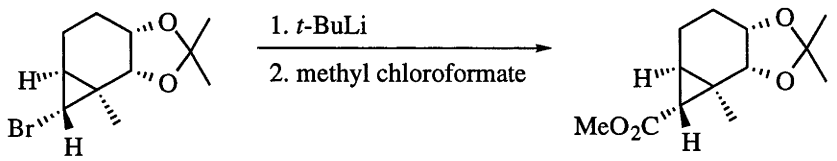
IR ν_{max} 2985, 2957, 2933, 1247, 1216 cm^{-1}.

EIMS (70eV) *m/z* 262, 260 ($M^{+\cdot}$, 17, 16), 247, 245 [$(M\text{-}H_3C\cdot)^+$, 50, 34], 183, 181 [$(M\text{-}Br\cdot)^+$, 45], 123 (77), 95 (100).

HRMS Found $M^{+\cdot}$, 262.0392. $C_{11}H_{17}{}^{81}BrO_2$ requires $M^{+\cdot}$, 262.0391. Found $M^{+\cdot}$, 260.0411. $C_{11}H_{17}{}^{79}BrO_2$ requires $M^{+\cdot}$, 260.0411.

Optical Rotation $[\alpha]_D{}^{20}$ + 16.6 ° (*c* 1.2, $CHCl_3$).

Methyl (3a*S*,5a*S*,6*S*,6a*R*,6b*R*)-2,2,6a-Trimethylhexahydrocyclopropa[*e*]-1,3-benzodioxolo-6(5a*H*)-carboxylate (140).



138 **140**

tert-Butyllithium (27.8 mL of a 1.7 M solution in pentane, 48.6 mmol) was added, dropwise, to a magnetically stirred solution of compound **138** (6.41 g, 24.3 mmol) in dry Et_2O (90 mL) maintained at -85 °C (acetone/liquid-nitrogen slush bath) under a nitrogen atmosphere. After 0.1 h methyl chloroformate (2.96 mL, 37 mmol) was

added, dropwise, and the reaction mixture was then warmed to 18 °C. The reaction mixture was diluted with water (100 mL) and Et_2O (200 mL) then the separated aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue subjected to flash chromatography (3:1 hexane/Et_2O elution). Concentration of the appropriate fractions, (R_f 0.4), then gave compound **140** (4.67 g, 80%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.26 (1H, d, J = 6.3 Hz), 4.17 (1H, m), 3.66 (3H, s), 2.13-2.01 (2H, m), 1.73-1.68 (2H, m), 1.50 (1H, d, J = 5.2 Hz), 1.46 (3H, s), 1.44-1.39 (1H, m), 1.33 (3H, s), 1.26 (3H, s).

^{13}C NMR (75.4 MHz) δ: 172.8 (C), 108.2 (C), 74.9 (CH), 72.1 (CH), 51.9 (CH_3), 28.6 (C), 28.5 (CH or CH_3), 27.5 (CH or CH_3), 25.7 (CH or CH_3), 24.3 (CH or CH_3), 21.7 (CH_2), 16.3 (CH_2), 15.3 (CH_3).

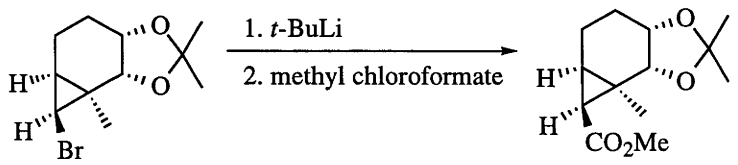
IR ν_{max} 2990, 2875, 1729, 1442, 1380 cm^{-1}.

EIMS (70eV) *m/z* 240 ($M^{+\cdot}$, 55), 225 [$(M-H_3C\cdot)^+$, 76], 182 {[$M-(CH_3)_2CO]^{+\cdot}$, 52}, 151 (72), 95 (100).

HRMS Found $M^{+\cdot}$, 240.1357. $C_{13}H_{20}O_4$ requires $M^{+\cdot}$, 240.1361.

Optical Rotation $[\alpha]_D^{20}$ + 2.1 ° (*c* 1.4, $CHCl_3$).

Methyl (3a*S*,5a*S*,6*R*,6a*R*,6b*R*)-2,2,6a-Trimethylhexahydrocyclopropa[*e*]-1,3-benzodioxolo-6(5a*H*)-carboxylate (141).



139 **141**

tert-Butyllithium (1.20 mL of a 1.7 M solution in pentane, 2.10 mmol) was added, dropwise, to a magnetically stirred solution of compound **139** (277 mg, 1.05 mmol) in dry Et_2O (3 mL) maintained at -85 °C (acetone/liquid-nitrogen slush bath) under a

nitrogen atmosphere. After 0.1 h methyl chloroformate (128 μL, 1.6 mmol) was added, dropwise, and the reaction mixture was then warmed to 18 °C. The reaction mixture was diluted with water (10 mL) and Et_2O (30 mL) then the separated aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue subjected to flash chromatography (2:1 hexane/Et_2O elution). Concentration of the appropriate fractions, (R_f 0.5), then gave compound **141** (210 mg, 83%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 4.35-4.31 (2H, m), 3.63 (3H, s), 1.96-1.91 (2H, m), 1.62-1.59 (2H, m), 1.51-1.42 (2H, m), 1.43 (3H, s), 1.31 (3H, s), 1.24 (3H, s).

^{13}C NMR (75.4 MHz) δ: 171.7 (C), 107.0 (C), 75.2 (CH), 72.9 (CH), 51.7 (CH_3), 31.9 (C), 29.9 (CH or CH_3), 28.5 (CH or CH_3), 27.6 (CH or CH_3), 27.4 (CH_2), 26.0 (CH or CH_3), 24.4 (CH or CH_3), 17.0 (CH_2).

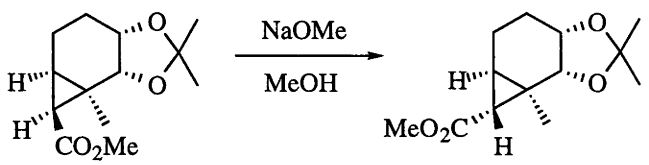
IR ν_{max} 2987, 2866, 1730, 1441, 1371 cm^{-1}.

EIMS (70eV) *m/z* 240 ($M^{+\cdot}$, 77), 225 [$(M\text{-}H_3C\cdot)^+$, 81], 182 {$[M\text{-}(CH_3)_2CO]^{+\cdot}$, 45}, 151 (80), 95 (100).

HRMS Found $M^{+\cdot}$, 240.1360. $C_{13}H_{20}O_4$ requires $M^{+\cdot}$, 240.1361.

Optical Rotation $[\alpha]_D^{20}$ + 43.4 ° (*c* 5.6, $CHCl_3$).

Methyl (3a*S*,5a*S*,6*S*,6a*R*,6b*R*)-2,2,6a-Trimethylhexahydrocyclopropa[*e*]-1,3-benzodioxolo-6(5a*H*)-carboxylate (140).

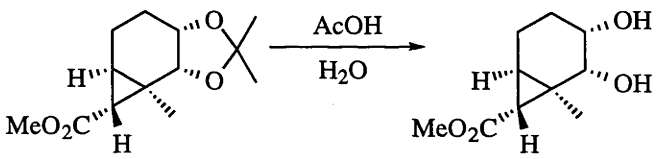


141 **140**

Small peices of sodium metal (1.2 g, 53 mmol) were added over 0.5 h to a round-bottomed flask containing anhydrous MeOH (20 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 1 h a solution of compound **141** (1.28 g, 5.3 mmol) in anhydrous MeOH (5 mL) was added, dropwise, and the reaction mixture was

then heated at reflux for 16 h. The cooled reaction mixture was treated with NH_4Cl (20 mL of a saturated aqueous solution) and EtOAc (100 mL) and the separated aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue subjected to flash chromatography (3:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.4), compound **140** (1.0 g, 78%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **140** produced under the conditions defined earlier (see page 142).

Methyl (1*R*,2*R*,3*S*,6*R*,7*R*)-2,3-Dihydroxy-1-methylbicyclo[4.1.0]-heptane-7-carboxylate (127).



140 **127**

A magnetically stirred solution of compound **140** (3.0 g, 12.5 mmol) in acetic acid (60 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was diluted with water (100 mL) and EtOAc (200 mL) then the separated aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue subjected to flash chromatography (1:1 EtOAc/Et_2O elution) to afford, after concentration of the appropriate fractions (R_f 0.6), compound **127** (1.79 g, 72%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 3.95 (1H, d, J = 3.0 Hz), 3.64 (3H, s), 3.56-3.52 (1H, m), 2.18-2.05 (2H, m), 1.62-1.55 (3H, m), 1.31 (1H, d, J = 4.6 Hz), 1.28 (3H, s), (signals due to two -**OH** protons not observed).

^{13}C NMR (75.4 MHz) δ: 172.8 (C), 70.9 (CH), 68.3 (CH), 51.9 (CH_3), 33.2 (C), 29.8 (CH or CH_3), 26.6 (CH or CH_3), 23.9 (CH_2), 20.8 (CH_2), 15.5 (CH or CH_3).

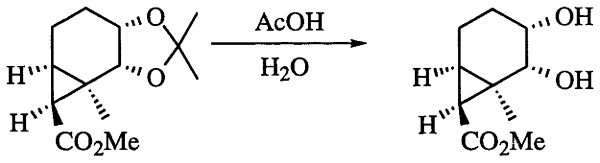
IR ν_{max} 3427 (b), 2952, 1728, 1206, 1046 cm^{-1}.

EIMS (70eV) *m/z* 182 [$(M-H_2O)^{+\cdot}$, 14], 150 (45), 122 (57), 97 (100), 87 (94).

HRMS Found $(M-H_2O)^{+\cdot}$, 182.0945. $C_{10}H_{16}O_4$ requires $(M-H_2O)^{+\cdot}$, 182.0942.

Optical Rotation $[\alpha]_D^{20}$ - 55.6 ° (*c* 1.6, $CHCl_3$).

Methyl (1*R*,2*R*,3*S*,6*R*,7*S*)-2,3-Dihydroxy-1-methylbicyclo[4.1.0]-heptane-7-carboxylate (142).



141 **142**

A magnetically stirred solution of compound **141** (4.0 g, 16.6 mmol) in acetic acid (80 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was diluted with water (100 mL) and EtOAc (200 mL) then the separated aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue subjected to flash chromatography (1:1 EtOAc/Et_2O elution) to afford, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallization (Et_2O) of this material then gave compound **142** (2.6 g, 78%) as colourless needles, m.p. 66-67 °C.

^{1}H NMR (300 MHz) δ: 3.93 (1H, d, *J* = 3.0 Hz), 3.92-3.89 (1H, m), 3.64 (3H, s), 2.30 (2H, bs), 2.03-1.98 (1H, m), 1.75-1.65 (3H, m), 1.46 (1H, d, *J* = 9.0 Hz), 1.36 (1H, t, *J* = 9.0 Hz), 1.25 (3H, s).

^{13}C NMR (75.4 MHz) δ: 172.1 (C), 69.9 (CH), 67.6 (CH), 51.7 (CH_3), 29.3 (CH or CH_3), 27.0 (C), 26.5 (CH_2), 25.5 (CH or CH_3), 24.5 (CH or CH_3), 15.5 (CH_2).

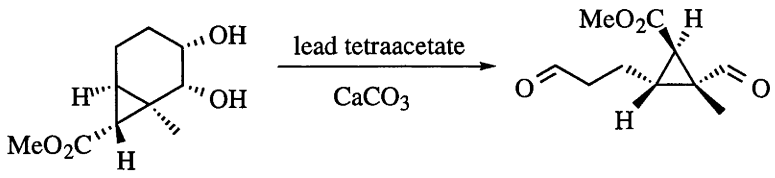
IR ν_{max} 3409 (b), 2951, 1725, 1442, 1171 cm^{-1}.

EIMS (70eV) *m/z* 182 [$(M\text{-}H_2O)^{+\cdot}$, 19], 150 (44), 122 (56), 97 (94), 87 (100).

HRMS Found $(M\text{-}H_2O)^{+\cdot}$, 182.0938. $C_{10}H_{16}O_4$ requires $(M\text{-}H_2O)^{+\cdot}$, 182.0942.

Optical Rotation $[\alpha]_D^{20}$ + 69.3 ° (*c* 12.0, $CHCl_3$).

Methyl (1*R*,2*R*,3*R*)-2-Formyl-2-methyl-3-(3-oxopropyl)cyclopropane-carboxylate (126).



127 **126**

A solution of lead tetraacetate (265 mg, 0.902 mmol) in dry CH_2Cl_2 (3 mL) was added, dropwise, to a magnetically stirred mixture of compound **127** (56 mg, 0.28 mmol) and calcium carbonate (338 mg, 3.4 mmol) in dry CH_2Cl_2 (3 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.75 h the reaction mixture was quenched with Et_2O (20 mL) then filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to yield compound **126** (51 mg, 91%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.75 (1H, d, *J* = 2.4 Hz), 9.37 (1H, s), 3.70 (3H, s), 2.55-2.51 (2H, m), 2.13 (1H, d, *J* = 6.0 Hz), 2.07-1.81 (3H, m), 1.41 (3H, s).

^{13}C NMR (75.4 MHz) δ: 201.0 (CH), 200.0 (CH), 170.2 (C), 52.4 (CH_3), 43.5 (CH_2), 39.5 (C), 35.7 (CH), 33.0 (CH), 19.5 (CH_3), 13.1 (CH_2).

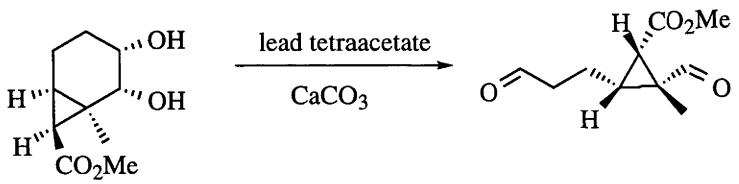
IR ν_{max} 2956, 1725, 1699, 1202, 1175 cm^{-1}.

EIMS (70eV) *m/z* 197 [$(M\text{-}H\cdot)^+$, 3], 183 [$(M\text{-}H_3C\cdot)^+$, 16], 155 (66), 139 (25), 127 (70), 109 (82), 95 (100).

HRMS Found $(M\text{-}H\cdot)^+$, 197.0818. $C_{10}H_{14}O_4$ requires $(M\text{-}H\cdot)^+$, 197.0813.

Optical Rotation $[\alpha]_D^{20}$ - 116.1 ° (*c* 4.1, $CHCl_3$).

Methyl (1*S*,2*R*,3*R*)-2-Formyl-2-methyl-3-(3-oxopropyl)cyclopropane-carboxylate (143).



142 **143**

A solution of lead tetraacetate (396 mg, 0.902 mmol) in dry CH_2Cl_2 (4 mL) was added, dropwise, to a magnetically stirred suspension of compound **142** (84 mg, 0.42 mmol) and calcium carbonate (504 mg, 5.0 mmol) in dry CH_2Cl_2 (7 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.75 h the reaction mixture was quenched with Et_2O (20 mL) then filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to yield compound **143** (80 mg, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.82 (1H, s), 9.77 (1H, d, J = 1.0 Hz), 3.70 (3H, s), 2.57 (2H, apparent t, J = 6.6 Hz), 2.39-2.30 (2H, m), 2.13 (1H, d, J = 8.9 Hz), 1.72-1.70 (1H, m), 1.22 (3H, s).

^{13}C NMR (75.4 MHz) δ: 201.3 (CH), 201.2 (CH), 170.5 (C), 52.6 (CH_3), 43.8 (CH_2), 37.1 (C), 35.8 (CH), 34.9 (CH), 19.8 (CH_3), 15.8 (CH_2).

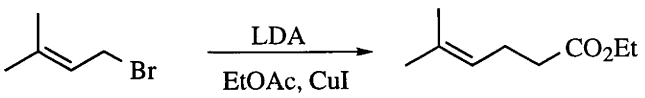
IR ν_{max} 2955, 1726, 1441, 1200, 1172 cm^{-1}.

EIMS (70eV) *m/z* 197 [(M-H·)$^+$, 1], 155 (16), 139 (25), 127 (26), 95 (100).

HRMS Found (M-H·)$^+$, 197.0819. $C_{10}H_{14}O_4$ requires (M-H·)$^+$, 197.0813.

Optical Rotation $[\alpha]_D^{20}$ + 15.0 ° (*c* 2.4, $CHCl_3$).

Ethyl 5-Methylhex-4-enoate (144).

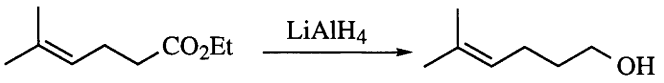


130 **144**

n-Butyllithium (30.0 mL of a 2.5 M solution in hexane, 74.6 mmol) was added, dropwise, to a magnetically stirred solution of diisopropylamine (10.5 mL, 74.6 mmol) in dry THF (30 mL) maintained at -78 °C (acetone/dry-ice slush bath) under a nitrogen atmosphere. The resulting mixture was warmed to 18 °C then kept at 0 °C for 0.2 h before being re-cooled to -78 °C.

The solution of lithium diisopropylamine thus formed was transferred, *via* cannula, to a magnetically stirred suspension of dry EtOAc (7.3 mL, 74.6 mmol) and cuprous iodide (28.3 g, 149.2 mmol) in dry THF (135 mL) maintained at -110 °C (EtOH/liquid-nitrogen slush bath) under a nitrogen atmosphere. The resulting tan-coloured suspension was stirred at -30 °C for 0.5 h then a solution of 4-bromo-2-methylbut-2-ene (**130**) (4.3 mL, 37.3 mmol) in dry THF (30 mL) was added dropwise. The reaction mixture was warmed to 18 °C then poured into water (800 mL). After NH_4Cl (200 g, 3.8 mol) had been added to the resulting mixture the separated aqueous phase was extracted with Et_2O (2 x 500 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield compound **144** (6.0 g, 97%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

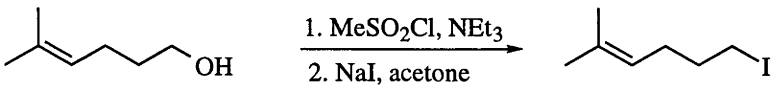
5-Methylhex-4-en-1-ol (145).



144 **145**

A solution of compound **144** (16.7 g, 100 mmol) in dry Et_2O (50 mL) was added, dropwise, to a magnetically stirred suspension of lithium aluminium hydride (4.2 g, 110 mmol) in dry Et_2O (70 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was stirred at 18 °C for 6 h then treated, sequentially, with water (13 mL) and sodium hydroxide (13 mL of a 15% aqueous solution). The resulting suspension was filtered and the solids thus retained were washed successively with Et_2O (400 mL) and hot $CHCl_3$ (400 mL). The combined filtrates were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield compound **145** (10.0 g, 88%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

6-Iodo-2-methylhex-2-ene (146).

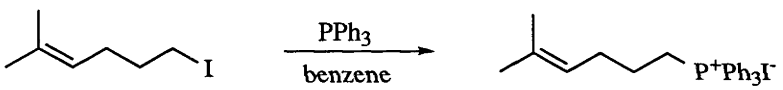


145 **146**

Methanesulfonyl chloride (7.4 mL, 96 mmol) was added, dropwise, to a magnetically stirred solution of compound **145** (10.0 g, 88 mmol) and triethylamine (18.6 mL, 134 mmol) in dry CH_2Cl_2 (110 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.25 h the reaction mixture was diluted with ice-cold water (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic phases were washed with cold HCl (1 x 200 mL of a 10% aqueous solution), $NaHCO_3$ (1 x 300 mL of a saturated aqueous solution) and NaCl (1 x 100

mL of a saturated aqueous solution). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. This material was added to a magnetically stirred solution of sodium iodide (22.0 g, 146 mmol) in dry acetone (200 mL) maintained at 18 °C under a nitrogen atmosphere. After stirring for 16 h the reaction mixture was diluted with pentane (200 mL) and the resulting mixture filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (pentane elution). Concentration of the appropriate fractions (R_f 0.7) afforded compound **146** (12.3 g, 62% from **145**) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

(2-Methylhex-2-ene)triphenylphosphonium iodide (129).



146 **129**

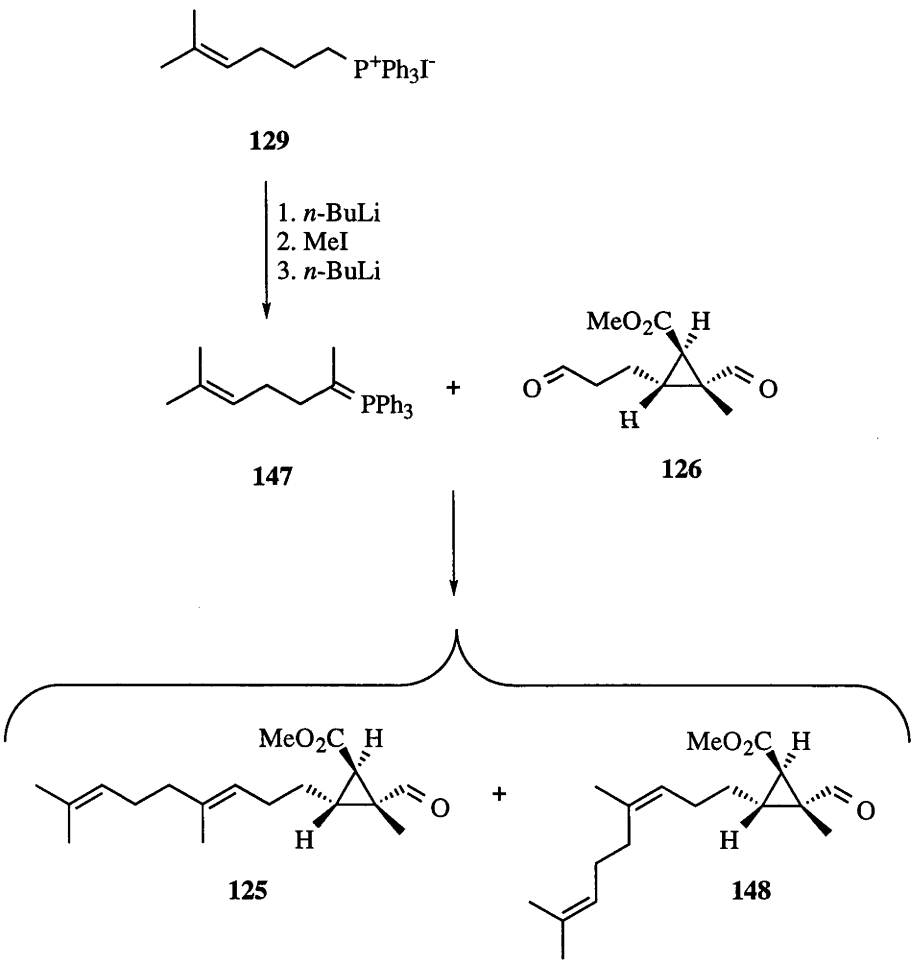
A magnetically stirred solution of compound **146** (5.3 g, 23.6 mmol) and triphenylphosphine (7.71 g, 29.2 mmol) in dry benzene (4 mL) that was protected from light with aluminium foil was stirred at 18 °C under a nitrogen atmosphere for 7 days. The resulting cloudy reaction mixture was poured into Et_2O (150 mL) and the precipitated solids removed by vacuum filtration. This material was dried under vacuum (10^{-3} Torr) to yield compound **129** (5.2 g, 45%) as a white powder, m.p. 142-143 °C (lit.[136] m.p. 142-143 °C).

^{1}H NMR (300 MHz) δ: 7.81-7.26 (18H, m), 4.97 (1H, m), 3.59-3.53 (2H, m), 2.33-2.26 (2H, m), 1.69-1.59 (2H, m), 1.62 (3H, s), 1.54 (3H, s).

^{13}C NMR (75.4 MHz) δ: 135.4 (CH), 134.7 (C), 133.9-133.7 (d, J = 10.0 Hz, CH), 130.9-130.7 (d, J = 12.5 Hz, CH), 122.1 (CH), 118.8 (C), 117.7 (C), 28.9-28.6 (d, J = 16.0 Hz, CH_2), 26.0 (CH_3), 22.9 (CH_2), 22.3 (CH_2), 18.4 (CH_3).

^{31}P NMR (121.4 MHz) δ: 25.1 (1H, s).

Methyl 3-[(3'*E*)-4',8'-Dimethylnona-3',7'-dienyl]-(1*R*,2*R*,3*R*)-2-formyl-2-methylcyclopropanecarboxylate (125) and Methyl 3-[(3'*Z*)-4',8'-Dimethylnona-3',7'-dienyl]-(1*R*,2*R*,3*R*)-2-formyl-2-methylcyclopropane-carboxylate (148).



n-Butyllithium (573 μL of a 1.6 M solution in hexane, 0.92 mmol) was added, dropwise, to a magnetically stirred suspension of (2-methyl-2-hexene)-triphenylphosphonium iodide (**129**) (443 mg, 0.92 mmol) in dry THF (10 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.25 h, methyl iodide

(59 μL, 0.92 mmol) was added, dropwise, to the orange-coloured reaction mixture. Stirring was continued for an additional 0.25 h before a second aliquot of *n*-butyllithium (573 μL of a 1.6 M solution in hexane, 0.92 mmol) was added. After an additional 0.25 h, the red-coloured reaction mixture was cooled to -78 °C (acetone/dry-ice slush bath) and after 0.25 h it was transferred, *via* cannula, to a magnetically stirred solution of compound **126** (180 mg, 0.92 mmol) in dry THF (3 mL) maintained at -78 °C (acetone/dry-ice slush bath) under a nitrogen atmosphere. The reaction mixture was warmed to 18 °C then quenched with solid NH_4Cl (*ca.* 500 mg). The resulting mixture was diluted with Et_2O (100 mL) then filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to give a pale-yellow oil which was subjected to flash chromatography (3:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f 0.5) then gave a *ca.* 2:1 mixture (as determined by ^1H NMR and ^{13}C NMR analysis) of compounds **125** and **148** (222 mg, 83%) as a clear, colourless oil.

^1H NMR (300 MHz) δ: 9.26 (1H, s), 9.25 (1H, s), 5.17-5.00 (4H, m), 3.70 (6H, s), 2.33 (2H, d, J = 6.5 Hz), 2.06-2.02 (8H, m), 1.98-1.96 (2H, m), 1.67 (6H, s), 1.60 (6H, s), 1.58 (6H, s), 1.39 (6H, s).

^{13}C NMR (75.4 MHz) δ: 199.9 (CH), 199.8 (CH), 170.6 (C), 136.8 (C), 136.7 (C), 131.9 (C), 131.6 (C), 124.4 (CH_2), 124.3 (CH_2), 123.7 (CH_2), 122.7 (CH_2), 52.2 (CH_3), 39.9 (CH_2), 39.6 (CH_2), 39.5 (CH), 36.3 (CH), 32.8 (CH), 32.7 (CH), 32.1 (CH_2), 31.1 (CH), 27.8 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 25.9 (CH_3), 23.6 (Z-CH_3), 17.9 (CH_3), 17.8 (CH_3), 16.2 (CH_3), 12.9 (CH_3).

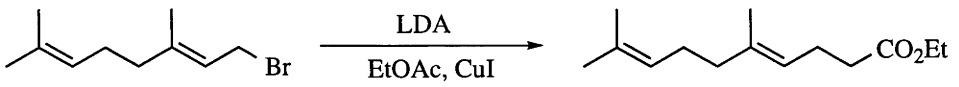
IR ν_{max} 2954, 2930, 1735, 1713 cm^{-1}.

EIMS (70eV) *m/z* 292 ($M^{+\cdot}$, 3), 249 (22), 217 (21), 163 (31), 95 (49), 69 (100).

HRMS Found $M^{+\cdot}$, 292.2040 $C_{18}H_{28}O_3$ requires $M^{+\cdot}$, 292.2038.

Optical Rotation $[\alpha]_D^{20}$ - 107.7 ° (*c* 1.3, $CHCl_3$).

Ethyl (4*E*)-5,9-Dimethyldeca-4,8-dienoate (149).

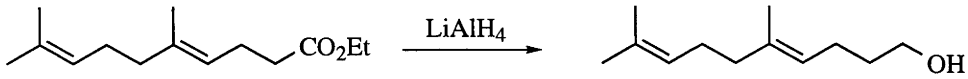


132 **149**

n-Butyllithium (74.0 mL of a 2.5 M solution in hexane, 180 mmol) was added, dropwise, to a magnetically stirred solution of diisopropylamine (26.0 mL, 184 mmol) in dry THF (75 mL) maintained at -78 °C (acetone/dry-ice slush bath) under a nitrogen atmosphere. The resulting mixture was warmed to 18 °C then kept at 0 °C for 0.2 h before being re-cooled to -78 °C.

The solution of lithium diisopropylamine thus-formed was transferred, *via* cannula, to a magnetically stirred suspension of dry EtOAc (18.0 mL, 184 mmol) and cuprous iodide (70 g, 368 mmol) in dry THF (270 mL) maintained at -110 °C (EtOH/liquid-nitrogen slush bath) under a nitrogen atmosphere. The resulting tan-coloured suspension was stirred at -30 °C for 0.5 h then a solution of geranyl bromide (**132**) (20.0 g, 92 mmol) in dry THF (30 mL) was added, dropwise, and the reaction mixture was warmed to 18 °C and the reaction mixture was poured into water (1.5 litres). After NH_4Cl (400 g, 7.6 mol) had been added to the resulting mixture the separated aqueous phase was extracted with Et_2O (2 x 800 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield compound **149** (20.5 g, 100%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

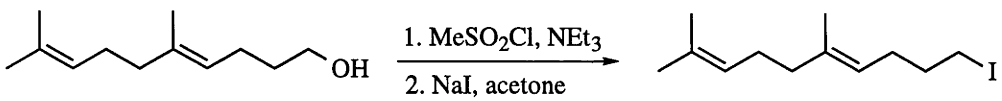
(4*E*)-5,9-Dimethyldeca-4,8-dien-1-ol (150).



149 **150**

A solution of compound **149** (20.5 g, 92 mmol) in dry Et_2O (50 mL) was added, dropwise, to a magnetically stirred suspension of lithium aluminium hydride (3.9 g, 101 mmol) in dry Et_2O (70 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was stirred at 18 °C for 6 h then treated, sequentially, with water (12 mL) and sodium hydroxide (12 mL of a 15% aqueous solution). The resulting suspension was filtered and the solids thus retained were washed successively with Et_2O (350 mL) and hot $CHCl_3$ (350 mL). The combined filtrates were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield compound **150** (16.7 g, 100%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

(6*E*)-10-Iodo-2,6-dimethyldeca-2,6-diene (151).

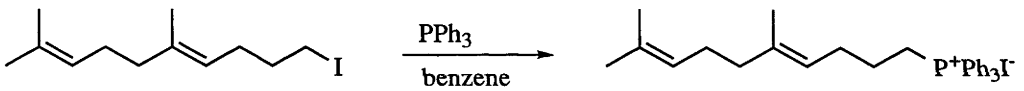


150 **151**

Methanesulfonyl chloride (7.1 mL, 92 mmol) was added, dropwise, to a magnetically stirred solution of compound **150** (16.8 g, 92 mmol) and triethylamine (17.8 mL, 128 mmol) in dry CH_2Cl_2 (110 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.25 h the reaction mixture was diluted with ice-cold water (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic phases were washed with cold HCl (1 x 200 mL of a 10% aqueous solution), $NaHCO_3$ (1 x 300 mL of a saturated aqueous solution) and NaCl (1 x 100

mL of a saturated aqueous solution). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. This material was added to a magnetically stirred solution of sodium iodide (22.0 g, 146 mmol) in dry acetone (200 mL) maintained at 18 °C under a nitrogen atmosphere. After stirring for 16 h the reaction mixture was diluted with pentane (200 mL) and the resulting mixture filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (pentane elution). Concentration of the appropriate fractions (R_f 0.6) afforded compound **151** (13.0 g, 48% from **150**) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[136] This material was used, without purification, in the next step of the reaction sequence.

[(4*E*)-5,9-Dimethyl-deca-4,8-dien]triphenylphosphonium iodide (129).



151 **131**

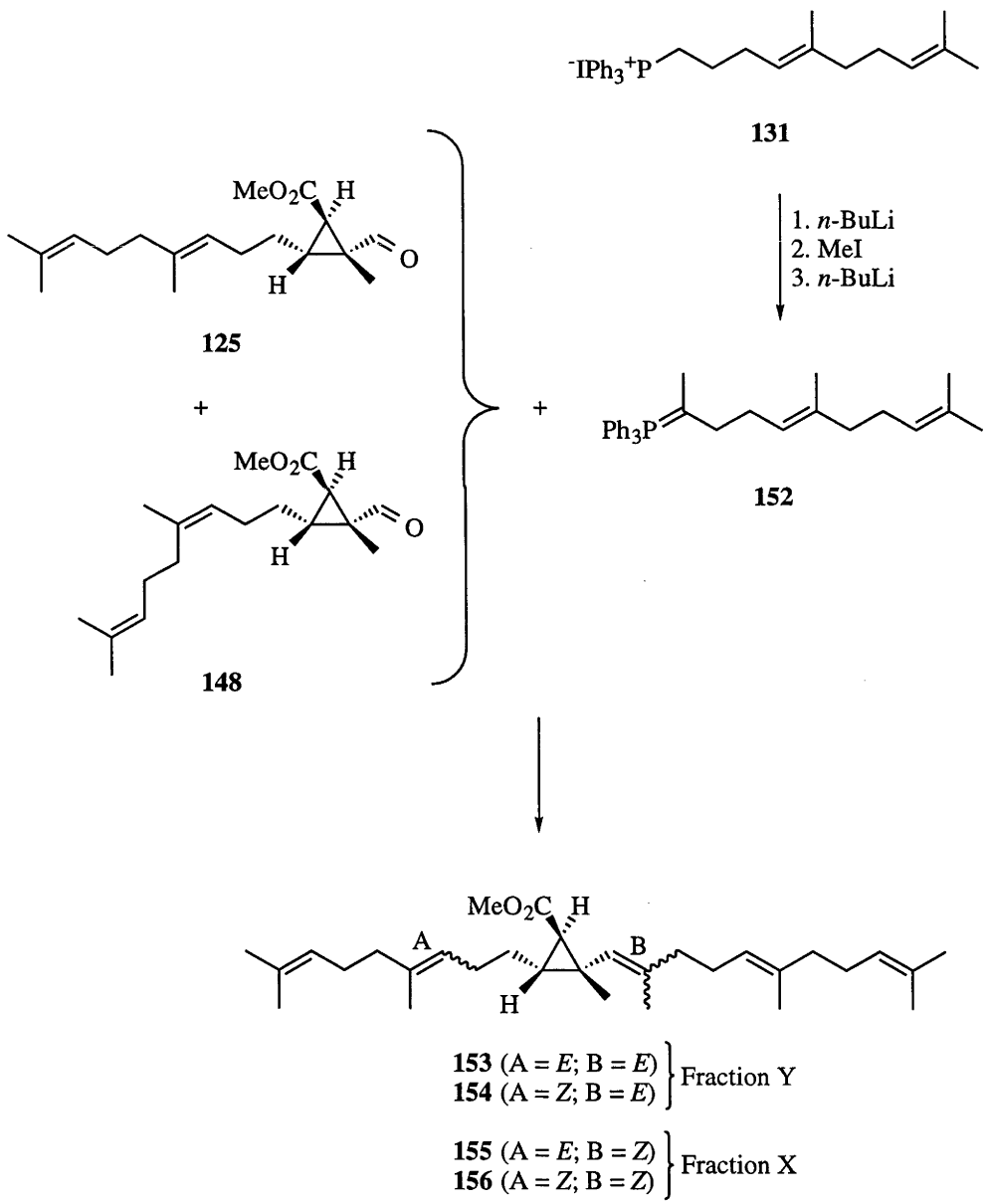
A magnetically stirred solution of compound **151** (11.0 g, 37.7 mmol) and triphenylphosphine (13.0 g, 49.0 mmol) in dry benzene (7 mL) that was protected from light with aluminium foil was stirred at 18 °C under a nitrogen atmosphere for 7 days. The resulting cloudy reaction mixture was poured into Et_2O (150 mL) and the precipitated solids removed by vacuum filtration. This material was dried under vacuum (10^{-3} Torr) to yield compound **131** (13.0 g, 63%) as a white powder, m.p. 97-98 °C (lit.[135] m.p. 96-97 °C).

^{1}H NMR (300 MHz) δ: 7.77-7.66 (15H, m), 7.40-7.38 (3H, m), 5.01-4.99 (2H, m), 3.70-3.68 (2H), 3.59-3.53 (2H, m), 2.36-2.33 (2H, m), 2.02-1.96 (4H, m), 1.70-1.66 (2H, m), 1.57 (6H, s), 1.54 (3H, s).

^{13}C NMR (75.4 MHz) δ: 137.9 (C), 135.2-1.35.1 (d, *J* = 2.1 Hz, CH), 133.6-133.4 (d, *J* = 10.2 Hz, CH), 131.2 (CH), 130.5-130.4 (d, *J* = 12.6 Hz, CH), 123.9 (CH), 121.5 (CH), 118.3 (C), 117.2 (C), 39.4 (CH_2), 28.2-28.1 (d, *J* = 16.4 Hz, CH_2), 26.3 (CH_2), 25.6 (CH_3), 22.4 (CH_2), 17.5 (CH_3), 16.4 (CH_3).

^{31}P NMR (121.4 MHz) δ: 22.3 (1H, s).

Methyl 2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)-cyclopropanecarboxylate (153), Methyl 2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)-cyclopropanecarboxylate (154), Methyl 2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)-cyclopropanecarboxylate (155) and Methyl 2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)-cyclopropanecarboxylate (156).



n-Butyllithium (979 μL of a 1.6 M solution in hexane, 1.6 mmol) was added, dropwise, to a magnetically stirred suspension of [(*E*)-5,9-dimethyl-4,8-decadienyl]triphenylphosphonium iodide (**131**) (863 mg, 1.6 mmol) in dry THF (18 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 0.25 h methyl iodide (101 μL, 0.92 mmol) was added, dropwise, to the orange-coloured reaction mixture. Stirring was continued for an additional 0.25 h before a second aliquot of *n*-butyllithium (979 μL of a 1.6 M solution in hexane, 1.6 mmol) was added. After an additional 0.25 h, the red-coloured reaction mixture was transferred *via* cannula to a magnetically stirred solution of a *ca.* 2:1 mixture of compounds **125** and **148** (228 mg, 0.78 mmol) in dry THF (4 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The mixture was warmed to 18 °C then quenched with solid NH_4Cl (*ca.* 500 mg). The resulting mixture was diluted with Et_2O (100 mL) then filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to provide a pale-yellow oil which was subjected to flash chromatography (3:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f 0.5) then gave a *ca.* 4:3:3:2 mixture (as determined by ^{13}C-^{1}H 2D HETCOR NMR spectroscopic techniques) of compounds **153-156** (258 mg, 73%) as a clear, colourless oil. Subjection of this material to preparative HPLC (μ-Porasil™ column, 100:1 hexane:*tert*-butyl methyl ether elution, flow rate = 8 mL/min) afforded two fractions (X and Y).

Concentration of the fraction X (R_t 18.6 min) gave a *ca.* 2:1 mixture of compounds **155** and **156** (156 mg, 44%).

^{1}H NMR (300 MHz) δ: 5.29 (1H, s), 5.15-5.07 (4H, m), 3.67 (3H, s), 2.49-1.95 (16H, m), 1.68, 1.62 , 1.60, 1.59 (21H, singlets, corresponding to 7 methyl group protons), 1.56-1.24 (2H, m), 1.22 (3H, s).

^{13}C NMR (75.4 MHz) δ: 173.6 (C), 140.9 (C), 135.8 (C), 135.5 (C), 131.9 (C), 131.7 (C), 126.4 (CH), 126.3 (CH), 124.9 (CH), 124.7 (CH), 124.7 (CH), 124.6 (CH), 124.4 (CH), 124.1 (CH), 51.7 (CH_3), 40.1 (CH_2), 40.0 (CH_2), 34.0 (CH or CH_3), 32.9 (CH or CH_3), 32.8 (CH or CH_3), 32.7 (CH_2), 32.2 (CH_2), 31.9 (CH_2),

30.7 (CH_2), 30.6 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 26.0 (CH_3), 23.8 (*Z*-CH_3), 23.0 (C), 22.9 (*Z*-CH_3), 20.5 (CH_3), 18.0 (CH_3), 17.9 (CH_3), 16.3 (CH_3).

IR ν_{max} 2965, 2924, 2856, 1731, 1440, 1158 cm^{-1}.

EIMS (70eV) *m/z* 454 ($M^{+\cdot}$, 14), 385 [$(M\text{-}H_9C_5\cdot)^+$, 9], 317 (7), 285 (5), 257 (10), 247 (8).

HRMS Found $M^{+\cdot}$, 454.3806. $C_{31}H_{50}O_2$ requires $M^{+\cdot}$, 454.3810.

Optical Rotation $[\alpha]_D^{20}$ - 13.9 ° (*c* 7.5, $CHCl_3$).

Concentration of the fraction Y (R_t 21.2 min) gave a *ca.* 2:1 mixture compounds **153** and **154** (138 mg, 39%).

^{1}H NMR (300 MHz) δ: 5.29 (1H, s), 5.10-5.06 (4H, m), 3.69 (3H, s), 2.07-1.97 (16H, m), 1.70, 1.68, 1.59, 1.59 (21H, singlets, corresponding to 7 methyl group protons), 1.56-1.24 (2H, m), 1.22 (3H, s).

^{13}C NMR (75.4 MHz) δ: 173.7 (C), 140.8 (C), 135.9 (C), 135.7 (C), 135.5 (C), 131.9 (C), 131.6 (C), 125.7 (CH), 125.7 (CH), 124.9 (CH), 124.6 (CH), 124.1 (CH), 124.1 (CH), 51.7 (CH_3), 40.0 (CH_2), 39.6 (CH_2), 34.0 (CH or CH_3), 33.3 (CH or CH_3), 33.2 (CH or CH_3), 32.2 (CH_2), 30.9 (CH_2), 30.9 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 27.0 (CH_2), 26.7 (CH_2), 26.0 (CH_3), 23.7 (*Z*-CH_3), 23.0 (C), 19.7 (CH_3), 18.0 (CH_3), 17.1 (CH_3), 16.4 (CH_3), 16.3 (CH_3).

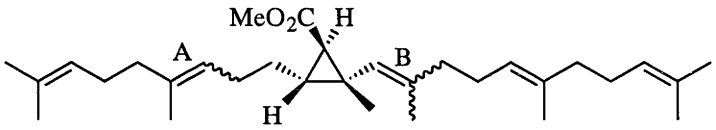
IR ν_{max} 2965, 2924, 2856, 1731, 1440, 1158 cm^{-1}.

EIMS (70eV) *m/z* 454 ($M^{+\cdot}$, 22), 385 [$(M\text{-}H_9C_5\cdot)^+$, 14], 317 (10), 285 (9), 257 (13), 247 (7).

HRMS Found $M^{+\cdot}$, 454.3810. $C_{31}H_{50}O_2$ requires $M^{+\cdot}$, 454.3810.

Optical Rotation $[\alpha]_D^{20}$ - 23.3 ° (*c* 1.4, $CHCl_3$).

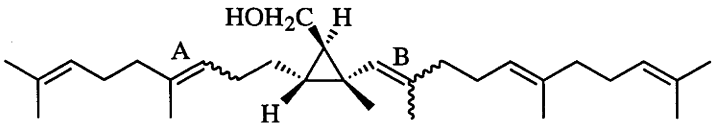
2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)cyclopropanemethanol (157), 2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)cyclopropanemethanol (158), 2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)cyclopropanemethanol (159) and 2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*S*,3*R*)cyclopropanemethanol (160).



153 (A = *E*; B = *E*)
154 (A = *Z*; B = *E*)
} Fraction Y

155 (A = *E*; B = *Z*)
156 (A = *Z*; B = *Z*)
} Fraction X

$LiAlH_4$



157 (A = *E*; B = *E*)
158 (A = *Z*; B = *E*)
} Fraction Y

159 (A = *E*; B = *Z*)
160 (A = *Z*; B = *Z*)
} Fraction X

A solution of compounds **155** and **156** (43 mg, 0.093 mmol) in dry Et_2O (1.0 mL) was added, dropwise, to a magnetically stirred suspension of lithium aluminium hydride (13 mg, 0.32 mmol) in Et_2O (1.5 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was stirred at 18 °C for 3 h then treated with NaCl (2 mL of a saturated aqueous solution) and citric acid (2 mL of a saturated aqueous solution). The resulting mixture was extracted with Et_2O (2 x 10 mL) then the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced

pressure to give a colourless oil which was subjected to flash chromatography (2:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f0.4) then gave a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **159** and **160** (36 mg, 93%) as a clear, colourless oil.

^1H NMR (300 MHz) δ: 5.29 (1H, s), 5.16-5.08 (4H, m), 3.69 (2H, d, J = 7.4 Hz), 2.26-1.96 (16H, m), 1.68, 1.67, 1.63, 1.61, 1.59 (21H, singlets, corresponding to 7 methyl group protons), 1.12 (3H, s), 0.86-0.77 (1H, m), 0.43-0.41 (1H, m).

^{13}C NMR (75.4 MHz) δ: 139.9 (C), 135.7 (C), 135.4 (C), 135.3 (C), 131.6 (C), 128.1 (CH), 128.0 (CH), 125.6 (CH), 124.8 (CH), 124.7 (CH), 124.6 (CH), 64.1 (CH_2), 40.1 (CH_2), 34.1 (CH or CH_3), 33.9 (CH or CH_3), 32.6 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 29.9 (CH or CH_3), 29.8 (CH_3), 28.5 (CH_2), 28.4 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 23.9 (C), 23.8 (C), 23.6 (*Z*-CH_3), 22.9 (*Z*-CH_3), 21.2 (CH_3), 17.9 (CH_3), 17.8 (CH_3), 16.3 (CH_3).

IR ν_{max} 2965, 2925, 2855, 1448 cm^{-1}.

EIMS (70eV) *m/z* 426 ($M^{+\cdot}$, 5), 339 (4), 289 (4), 271 (5), 217 (16).

HRMS Found $M^{+\cdot}$, 426.3868. $C_{30}H_{50}O$ requires $M^{+\cdot}$, 426.3861.

Optical Rotation $[\alpha]_D^{20}$ + 2.5 ° (*c* 5.8, $CHCl_3$).

Lithium aluminium hydride-promoted reduction of compounds **153** and **154** (58 mg, 0.13 mmol) in the same manner described above for compounds **155** and **156** gave a pale-yellow oil upon work-up. Subjection of this material to flash chromatography (2:1 hexane/Et_2O elution) afforded, after concentration of the appropriate fractions (R_f0.4) a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **157** and **158** (50 mg, 91%) as a clear, colourless oil.

^1H NMR (300 MHz) δ: 5.26 (1H, s), 5.16-5.06 (4H, m), 3.68 (2H, m), 2.08-1.93 (16H, m), 1.71, 1.68, 1.67 (21H, singlets, corresponding to 7 methyl group protons), 1.12 (3H, s), 0.74-0.70 (1H, m), 0.46-0.42 (1H, m).

^{13}C NMR (75.4 MHz) δ: 139.5 (C), 135.6 (C), 135.4 (C), 131.9 (C), 131.6 (C), 131.5 (C), 127.6 (CH), 125.7 (CH), 124.8 (CH), 124.7 (CH), 124.6 (CH), 124.5

(CH), 64.2 (CH_2), 40.1 (CH_2), 40.0 (CH_2), 33.8 (CH), 33.7 (CH), 32.3 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 30.0 (CH_2), 29.9 (CH_3), 28.5 (CH_2), 28.4 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 24.0 (C), 23.7 (*Z*-CH_3), 20.3 (CH_3), 18.0 (CH_3), 17.1 (CH_3), 16.4 (CH_3), 16.3 (CH_3).

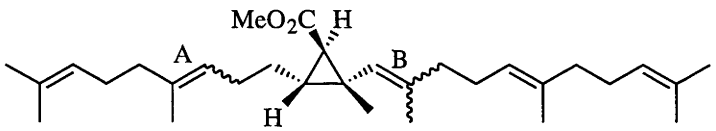
IR ν_{max} 2965, 2925, 2855, 1448 cm^{-1}.

EIMS (70eV) *m/z* 426 ($M^{+\cdot}$, 7), 339 (6), 289 (6), 271 (10), 217 (39).

HRMS Found $M^{+\cdot}$, 426.3858. $C_{30}H_{50}O$ requires $M^{+\cdot}$, 426.3861.

Optical Rotation $[\alpha]_D^{20}$ - 2.2 ° (*c* 1.1, $CHCl_3$).

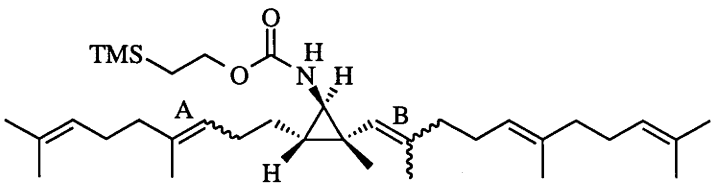
{2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropyl}-2-[(trimethylsilyl)ethyl]carboxamide (169), {2-[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropyl}-2-[(trimethylsilyl)-ethyl]-carboxamide (170), {2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropyl}-2-[(trimethylsilyl)-ethyl]carboxamide (171) and {2-[(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-2-methyl-3-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropyl}-2-[(trimethylsilyl)ethyl]-carboxamide (172).



153 (A = *E*; B = *E*)
154 (A = *Z*; B = *E*)
} Fraction Y

155 (A = *E*; B = *Z*)
156 (A = *Z*; B = *Z*)
} Fraction X

1. KOH, MeOH
2. $(PhO)_2PON_3$, $TMS(CH_2)_2OH$



169 (A = *E*; B = *E*)
170 (A = *Z*; B = *E*)
} Fraction Y

171 (A = *E*; B = *Z*)
172 (A = *Z*; B = *Z*)
} Fraction X

Potassium hydroxide (3.75 mL of a 1.2 M solution in MeOH, 4.5 mmol) was added to compounds **155** and **156** (58 mg, 0.125 mmol) and the resulting mixture was stirred at 18 °C for 16 h then treated, sequentially, with H_2O (4 mL) and HCl (3 mL of a 1M aqueous solution). The mixture thus obtained was extracted with CH_2Cl_2 (4 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and

concentrated under reduced pressure to give a pale-yellow oil (48 mg, 98%). This crude acid was dissolved in anhydrous toluene (100 μL) and the solution thus formed treated, dropwise, with triethylamine (15 μL, 0.12 mmol) and diphenyl phosphorazidate (23 μL, 0.12 mmol). The resulting solution was heated at 100 °C for 0.2 h then cooled to 50 °C and treated with 2-(trimethylsilyl)ethanol (30 μL, 0.12 mmol). After a further 16 h at 50 °C the reaction mixture was cooled then diluted with water (1 mL) and Et_2O (5 mL). The separated aqueous phase was extracted with Et_2O (5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil which was subjected to flash chromatography (6:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f 0.4) then gave a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **171** and **172** (41 mg, 62%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.30-5.09 (5H, m), 4.70 (1H, bs), 4.28 (2H, m), 2.42-2.12 (17H, m), 1.71, 1.67, 1.60 (21H, singlets, corresponding to 7 methyl group protons), 1.42 (1H, m), 1.10 (3H, s), 1.00 (2H, bs), 0.03 (9H, s).

^{13}C NMR (75.4 MHz) δ: 157.9 (C), 141.2 (C), 140.8 (C), 140.7 (C), 135.7 (C), 135.6 (C), 130.2 (CH), 130.0 (CH), 126.3 (CH), 125.5 (CH), 124.7 (CH), 124.6 (CH), 124.4 (CH), 124.0 (CH), 63.2 (CH_2), 41.6 (CH), 41.5 (CH), 40.0 (CH_2), 32.9 (CH_2), 32.5 (CH), 29.7 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 23.7 (Z-CH_3), 23.1 (C), 22.8 (Z-CH_3), 20.7 (CH_3), 20.6 (CH_3), 18.0 (CH_3), 16.3 (CH_3), -1.2 (CH_3).

IR ν_{max} 3450, 2950, 2920, 2840, 1700, 1500, 1370, 1245 cm^{-1}.

EIMS (70eV) *m/z* 555 ($M^{+\cdot}$, 4), 527 [$(M\text{-}CO)^{+\cdot}$, 14], 512 (20), 458 (35), 410 (27), 390 (51).

HRMS Found $M^{+\cdot}$, 555.4466. $C_{35}H_{61}NO_2Si$ requires $M^{+\cdot}$, 555.4471.

Optical Rotation $[\alpha]_D^{20}$ - 1.5 ° (*c* 4.6, $CHCl_3$).

Treatment of the mixture of esters **153** and **154** (73 mg, 0.156 mmol) in the same manner as described immediately above for isomers **155** and **156** gave a pale-yellow

oil upon work-up. This material was subjected to flash chromatography (6:1 hexane/Et_2O elution). After concentration of the appropriate fractions (R_f 0.3), a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **155** and **156** (46 mg, 73%) was obtained as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.30-5.09 (5H, m), 4.70 (1H, bs), 4.28 (2H, m), 2.42-2.12 (17H, m), 1.71, 1.67, 1.60 (21H, singlets, corresponding to 7 methyl group protons), 1.42 (1H, m), 1.10 (3H, s), 1.00 (2H, bs), 0.03 (9H, s).

^{13}C NMR (75.4 MHz) δ: 157.9 (C), 141.2 (C), 140.8 (C), 140.7 (C), 135.7 (C), 135.6 (C), 130.2 (CH), 130.0 (CH), 126.3 (CH), 125.5 (CH), 124.7 (CH), 124.6 (CH), 124.4 (CH), 124.0 (CH), 63.2 (CH_2), 41.6 (CH), 41.5 (CH), 40.0 (CH_2), 32.9 (CH_2), 32.5 (CH), 29.7 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 23.7 (Z-CH_3), 22.8 (Z-CH_3), 20.0 (CH_3), 19.9 (CH_3), 18.1 (C), 18.0 (CH_3), 16.3 (CH_3), -1.2 (CH_3).

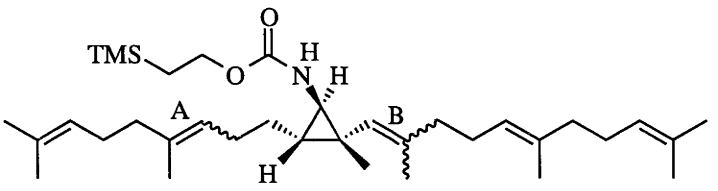
IR ν_{max} 3450, 2950, 2920, 2840, 1700, 1500, 1370, 1245 cm^{-1}.

EIMS (70eV) *m/z* 555 ($M^{+\cdot}$, 12), 527 [$(M\text{-}CO)^{+\cdot}$, 17], 512 (22), 458 (33), 410 (32), 390 (56).

HRMS Found $M^{+\cdot}$, 555.4466. $C_{35}H_{61}NO_2Si$ requires $M^{+\cdot}$, 555.4471.

Optical Rotation $[\alpha]_D^{20}$ - 6.9 ° (*c* 2.9, $CHCl_3$).

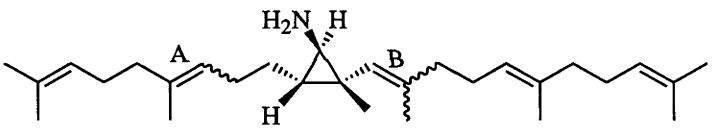
[(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-*N*-methyl-2-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropanamine (164), [(1'*E*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-*N*-methyl-2-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropanamine (173), [(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-*N*-methyl-2-[(3''*E*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropanamine (174) and [(1'*Z*,5'*E*)-2',6',10'-Trimethyl-1',5',9'-undecatrienyl]-*N*-methyl-2-[(3''*Z*)-4'',8''-dimethylnona-3'',7''-dienyl]-(1*R*,2*R*,3*S*)-cyclopropanamine (175).



169 (A = *E*; B = *E*)
170 (A = *Z*; B = *E*) } Fraction Y

171 (A = *E*; B = *Z*)
172 (A = *Z*; B = *Z*) } Fraction X

TBAF



164 (A = *E*; B = *E*)
173 (A = *Z*; B = *E*) } Fraction Y

174 (A = *E*; B = *Z*)
175 (A = *Z*; B = *Z*) } Fraction X

A solution of tetra-*n*-butylammonium fluoride hydrate (45 mg, 0.14 mmol) in THF (80 μL) was added, dropwise, to a magnetically stirred solution of compounds **171** and **172** (20 mg, 0.04 mmol) and the resulting mixture stirred at 50 °C for 1 h. The cooled reaction mixture was then diluted with water (1 mL) and Et_2O (5 mL). The separated aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (5:5:1 hexane/EtOAc/MeOH elution) which afforded, after concentration of the appropriate

fractions (R_f 0.6), a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **174** and **175** (9 mg, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.20-5.08 (5H, m), 2.17-1.99 (16H, m), 1.88 (1H, d, *J* = 3.8 Hz), 1.68, 1.67, 1.63, 1.60, (21H, singlets, corresponding to 7 methyl group protons), 1.36-1.07 (2H, m), 1.14 (3H).

^{13}C NMR (75.4 MHz) δ: 139.6 (C), 135.4 (C), 135.1 (C), 131.8 (C), 131.7 (C), 130.2 (CH), 128.1 (CH), 125.6 (CH), 124.8 (CH), 124.7 (CH), 124.6 (CH), 43.4 (CH), 40.0 (CH), 40.0 (CH_2), 33.3 (CH), 33.2 (CH_2), 32.3 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 26.0 (CH_3), 25.1 (C), 23.8 (*Z*-CH_3), 22.8 (*Z*-CH_3), 20.0 (CH_3), 18.0 (CH_3), 16.3 (CH_3).

IR ν_{max} 3400, 2970, 2940, 2870, 1740, 1660, 1460, 1380 cm^{-1}.

EIMS (70eV) *m/z* 411 ($M^{+\cdot}$, 3), 396 [$(M-H_3C\cdot)^+$, 6], 342 [$(M-H_9C_5\cdot)^+$, 81], 328 (24), 274 (28).

HRMS Found $M^{+\cdot}$, 411.3858. $C_{29}H_{49}NO$ requires $M^{+\cdot}$, 411.3865.

Optical Rotation $[\alpha]_D^{20}$ - 13.0 ° (*c* 1.0, $CHCl_3$).

Treatment of the mixture of carbamates **169** and **170** (46 mg, 0.08 mmol) in the same manner as described immediately above for isomers **171** and **172** gave a pale-yellow oil upon work-up. Subjection of this material to flash chromatography (5:5:1 hexane/EtOAc/MeOH elution) afforded, after concentration of the appropriate fractions (R_f 0.5) a *ca.* 2:1 mixture (as judged by ^{13}C NMR analysis) of compounds **164** and **173** (12 mg, 35%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.20-5.08 (5H, m), 2.17-1.99 (16H, m), 1.86 (1H, d, *J* = 3.7 Hz), 1.68, 1.65, 1.61, 1.59, (21H, singlets, corresponding to 7 methyl group protons), 1.38-1.09 (2H, m), 1.13 (3H).

^{13}C NMR (75.4 MHz) δ: 139.6 (C), 135.4 (C), 135.1 (C), 131.8 (C), 131.7 (C), 130.2 (CH), 128.1 (CH), 125.6 (CH), 124.8 (CH), 124.7 (CH), 124.6 (CH), 43.4 (CH), 39.5 (CH), 39.4 (CH_2), 33.5 (CH), 33.4 (CH_2), 32.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 28.3 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 26.5 (CH_2), 26.0

(CH_3), 25.2 (C), 23.8 (*Z*-CH_3), 19.2 (CH_3), 18.0 (CH_3), 17.5 (CH_3), 16.4 (CH_3), 16.3 (CH_3).

IR ν_{max} 3400, 2970, 2940, 2870, 1740, 1660, 1460, 1380 cm^{-1}.

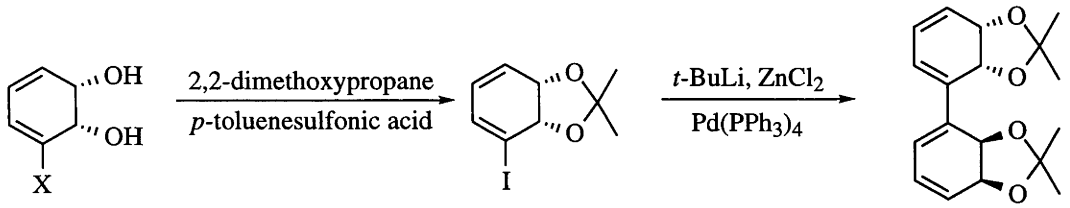
EIMS (70eV) *m/z* 411 ($M^{+\cdot}$, 4), 396 [$(M-H_3C\cdot)^+$, 6], 342 [$(M-H_9C_5\cdot)^+$, 100], 328 (32), 274 (36).

HRMS Found $M^{+\cdot}$, 411.3866. $C_{29}H_{49}NO$ requires $M^{+\cdot}$, 411.3865.

Optical Rotation $[\alpha]_D^{20}$ + 14.0 ° (*c* 0.9, $CHCl_3$).

6.5 Experimental Details Associated with Work Described in Chapter Five

Bis-Acetonide (203).



X (X=I) **202** **203**

p-Toluenesulfonic acid monohydrate (210 mg, 1.6 mmol) was added, in one portion, to a magnetically stirred solution of (1*S*,2*S*)-*cis*-3-iodo-3,5-cyclohexadiene-1,2-diol (**14**, X=I) (1.0 g, 4.2 mmol) in 2,2-dimethoxypropane (20 mL, 162 mmol) maintained at *ca.* -10 °C (salt-ice bath) under a nitrogen atmosphere. After 0.5 h the reaction mixture was diluted with triethylamine (0.5 mL) then concentrated under reduced pressure. The residue thus obtained was partitioned between Et_2O (100 mL) and water (30 mL) and the separated aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide compound **202**[168] (950 mg, 82%) as a pale-yellow oil. This material was used, without purification, in the next step of the reaction sequence.

tert-Butylyllithium (2.2 mL of a 1.7 M solution in pentane, 3.64 mmol) was added, dropwise, to a magnetically stirred solution of compound **202** (460 mg, 1.66 mmol) in dry THF (8 mL) maintained at -96 °C (acetone/liquid-nitrogen slush bath) under a nitrogen atmosphere. After 0.1 h a solution of flame-dried zinc chloride (252 mg, 1.66 mmol) in dry THF (2 mL) was added, dropwise, to the reaction mixture. The resulting solution was warmed to -30 °C over 0.5 h then a solution of compound **202** (460 mg, 1.66 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg, 0.086 mmol) in dry THF (0.5 mL) was added dropwise. After stirring at 18 °C for 6 h, the reaction mixture was diluted with water (5 mL) and Et_2O (70 mL). The separated aqueous phase was extracted with Et_2O (2 x 100 mL) and the combined organic phases were then dried

($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (25:25:1 hexane/Et_2O/triethylamine elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), compound **203** [254 mg, 40% from **14** (X=I)] as an unstable, clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.38 (2H, d, *J* = 6.1 Hz), 6.07 (2H, dd, *J* = 6.1, 1.5 Hz), 5.85 (2H, dd, *J* = 9.7 and 3.2 Hz), 4.82 (2H, dd, *J* = 8.3 and 3.2 Hz), 4.76 (2H, d, *J* = 8.3 Hz), 1.42 (6H, s), 1.37 (6H, s)

^{13}C NMR (75.4 MHz) δ: 134.1 (2xC), 127.2 (2xCH), 123.8 (2xCH), 121.3 (2xCH), 106.1 (2xC), 73.3 (2xCH), 71.1 (2xCH), 27.2 (2xCH_3), 25.5 (2xCH_3).

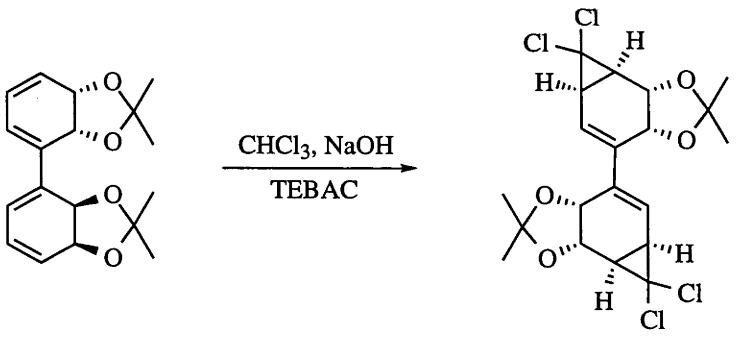
IR ν_{max} 2985, 2933, 1380, 1369, 1210 cm^{-1}.

EIMS (70eV) *m/z* 302 ($M^{+\cdot}$, 59), 244 {[M-$(CH_3)_2CO]^{+\cdot}$, 6}, 186 (100), 158 (69).

HRMS Found $M^{+\cdot}$, 302.1511. $C_{18}H_{22}O_4$ requires $M^{+\cdot}$, 302.1518.

Optical Rotation $[\alpha]_D^{20}$ + 278.0 ° (*c* 10.0, $CHCl_3$).

***Bis*-Acetonide (204).**



203 **204**

Sodium hydroxide (4 mL of a 50% w/w aqueous solution, 52.1 mmol) was added, dropwise, to a magnetically stirred solution of compound **203** (266 mg, 0.88 mmol) and benzyltriethylammonium chloride (20 mg, 0.086 mmol) in $CHCl_3$ (4 mL, 49.6 mmol) maintained at 5 °C (ice-bath). The resulting dark-brown reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (150 mL) and water (100 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the

combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (3:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallization (CH_3Cl_3/Et_2O) of this material then gave compound **204** (117 mg, 29%) as colourless needles, m.p. 209-210 °C.

^{1}H NMR (300 MHz) δ: 6.05-6.02 (2H, m), 4.74 (2H, d, *J* = 7.6 Hz), 4.66 (2H, d, *J* = 7.6 Hz), 2.35 (4H, s), 1.33 (6H, s), 1.25 (6H, s).

^{13}C NMR (75.4 MHz) δ: 139.6 (2xC), 118.6 (2xCH), 109.7 (2xC), 72.0 (2xCH), 69.4 (2xCH), 63.6 (2xC), 19.9 (2xCH or 2xCH_3), 28.7 (2xCH or 2xCH_3), 28.0 (2xCH or 2xCH_3), 26.9 (2xCH or 2xCH_3).

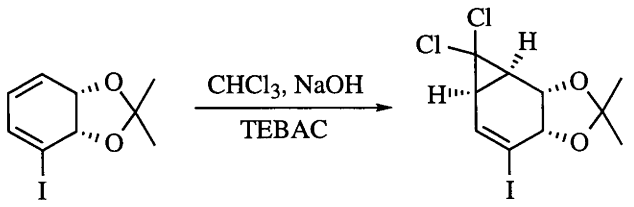
IR ν_{max} 2988, 2873, 23.9, 20.2, 1357, 1234, 1164, 1061 cm^{-1}.

EIMS (70eV) *m/z* 453, 451 [$(M\text{-}H_3C\cdot)^+$, 5, 7], 409 (14), 351 (16), 314 (100), 286 (32), 152 (58).

HRMS Found $(M\text{-}H_3C\cdot)^+$, 453.0015. $C_{20}H_{22}{}^{35}Cl_3{}^{37}ClO_4$ requires $(M\text{-}H_3C\cdot)^+$, 453.0004. Found $(M\text{-}H_3C\cdot)^+$, 451.0037. $C_{20}H_{22}{}^{35}Cl_4O_4$ requires $(M\text{-}H_3C\cdot)^+$, 451.0037.

Optical Rotation $[\alpha]_D{}^{20}$ - 132.9 ° (*c* 1.4, $CHCl_3$).

(3a*R*,5a*R*,6a*R*,6b*S*)-6,6-Dichloro-4-iodo-2,2-dimethyl-3a,5a,6a,6b-tetrahydro-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (205).



202 **205**

Sodium hydroxide (9.2 mL of a 50% w/w aqueous solution, 0.12 mol) was added, dropwise, to a magnetically stirred solution of compound **202** (2.53 g, 9.13 mmol) and benzyltriethylammonium chloride (50 mg, 0.22 mmol) in $CHCl_3$ (10 mL, 124.0 mmol) maintained at 5 °C (ice-bath). The resulting dark-brown reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (150 mL) and water (100 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (1:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), a white solid. Recrystallization (hexane/Et_2O) of this material then gave compound **205** (2.55 g, 78%) as colourless needles, m.p. 128-129 °C.

^{1}H NMR (300 MHz) δ: 6.68 (1H, d, *J* = 4.9 Hz), 4.71 (1H, d, *J* = 5.5 Hz), 4.71 (1H, d, *J* = 5.5 Hz), 2.43 (1H, dd, *J* = 9.6 and 1.6 Hz), 2.27 (1H, dd, *J* = 9.6 and 5.5 Hz), 1.45 (3H, s), 1.40 (3H, s).

^{13}C NMR (75.4 MHz) δ: 132.0 (CH), 110.2 (C), 103.5 (C), 76.1 (CH), 68.8 (CH), 31.3 (CH or CH_3), 29.2 (CH or CH_3), 27.8 (CH or CH_3), 26.6 (CH or CH_3), (one signal due to a quaternary carbon not observed).

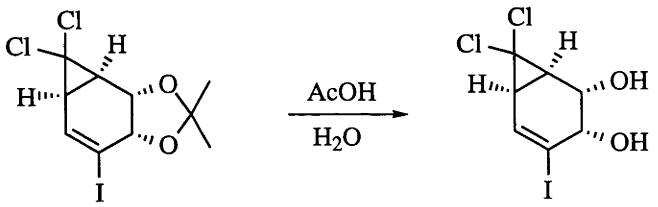
IR ν_{max} 2987 ,2890, 1366, 1251, 1220, 1060, 874 cm^{-1}.

EIMS (70eV) *m/z* 347, 345 [$(M\text{-}H_3C\cdot)^+$, 52, 46], 302 {$[M\text{-}(CH_3)_2CO]^{+\cdot}$, 80}, 285 (89), 267 (55), 175 (100).

Elemental Analysis Found: C, 33.32; H, 2.81; Cl, 19.39; I, 35.11; $C_{10}H_{11}Cl_2IO_2$ requires: C, 33.27; H, 3.07; Cl, 19.64; I, 35.15%.

Optical Rotation $[\alpha]_D^{20}$ + 8.0 ° (*c* 2.7, $CHCl_3$).

(1*S*,2*S*,3*S*,6*S*)-7,7-Dichloro-4-iodobicyclo[4.1.0]hept-4-ene-2,3-diol (206).



205 **206**

A magnetically stirred solution of compound **205** (450 mg, 1.37 mmol) in acetic acid (15 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was then diluted with water (50 mL) and EtOAc (100 mL) and the separated aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.4), a white solid. Recrystallization ($CHCl_3/Et_2O$) of this material then gave compound **206** (355 mg, 81%) as colourless needles, m.p. 124-125 °C.

^{1}H NMR (300 MHz) δ: 6.73 (1H, d, *J* = 4.5 Hz), 4.23 (2H, bs), 3.00-2.93 (1H, bd, *J* = 4.5 Hz), 2.31 (1H, dd, *J* = 10.2, 4.5 Hz), 2.20 (1H, d, *J* = 10.2 Hz), 1.73 (1H, bs).

^{13}C NMR (75.4 MHz) δ: 135.1 (CH), 104.2 (C), 73.3 (CH), 66.3 (CH), 65.2 (C), 33.3 (CH), 33.2 (CH).

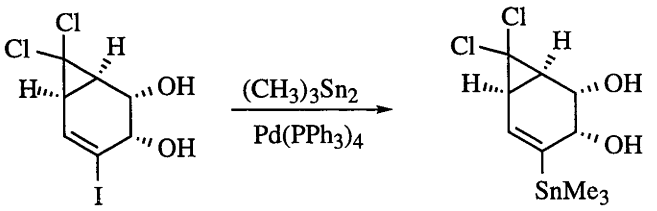
IR ν_{max} 3365 , 3295, 1345, 1255, 1070, 830, 795 cm^{-1}.

EIMS (70eV) *m/z* 322, 320 ($M^{+\cdot}$, 0.2, 0.1), 267 (24), 249 (23), 175 (100), 147 (43), 110 (77).

Elemental Analysis Found: C, 25.90; H, 2.02; Cl, 21.75; I, 39.61.; $C_7H_7Cl_2IO_2$ requires: C, 26.20; H, 2.20; Cl, 22.09; I, 39.54%.

Optical Rotation $[\alpha]_D^{20}$ - 93.7 ° (*c* 1.9, acetone).

(1*R*,2*R*,3*R*,6*S*)-7,7-Dichloro-4-(trimethylstannyl)bicyclo[4.1.0]hept-4-ene-2,3-diol (207).



206 **207**

A solution of hexamethylditin (3.0 mL, 10.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (350 mg, 0.30 mmol) in dry THF (5 mL) was added, dropwise, to a magnetically stirred solution of compound **206** (2.92 g, 9.12 mmol) in dry THF (100 mL) maintained at 18 °C under a nitrogen atmosphere. The resulting dark-brown reaction mixture was heated at 50 °C for 16 h then cooled and diluted with water (10 mL) and Et_2O (20 mL). The separated aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (1:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallization (hexane/Et_2O) of this material then gave compound **207** (2.36 g, 73%) as colourless needles, m.p. 72-73 °C.

^{1}H NMR (300 MHz) δ: 6.17-6.15 (1H, m), 4.49-4.21 (2H, m), 2.59 (1H, d, *J* = 9.4 Hz), 2.35-2.28 (3H, m), 0.18 (9H, t, *J* = 27.8 Hz).

SFORD ^{13}C NMR (75.4 MHz) δ: 149.0 (C), 130.3 (t, *J* = 15.6 Hz, CH), 69.5 (CH), 64.2 (C), 63.2 (t, *J* = 15.6 Hz, CH), 34.1 (CH), 29.3 (t, *J* = 19.3 Hz, CH), -8.63 (t, *J* = 177 Hz, CH_3).

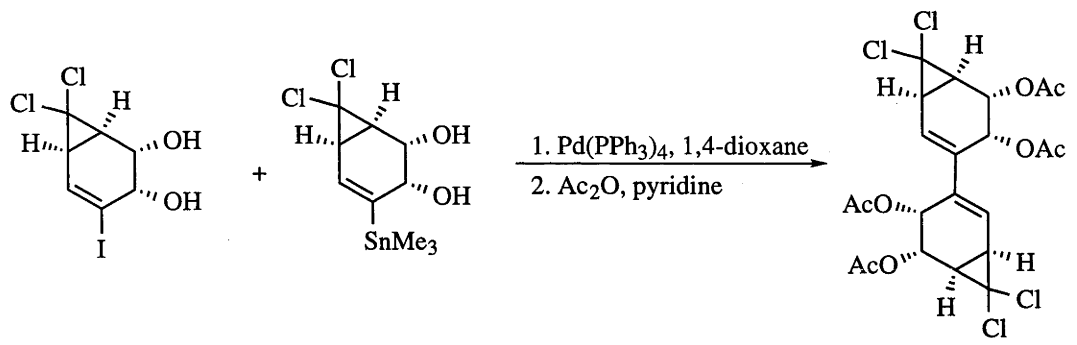
IR ν_{max} 3350 ,1240, 1060, 1035, 770 cm^{-1}.

EIMS (70eV) *m/z* 345, 343, 341 [$(M\text{-}H_3C\cdot)^+$, 65, 73, 50], 325 (60), 185 (94), 165 (100).

Elemental Analysis Found: C, 33.29; H, 4.28; Cl, 19.60.; $C_{10}H_{16}Cl_2O_2Sn$ requires: C, 33.57; H, 4.51; Cl, 19.82%.

Optical Rotation $[\alpha]_D^{20}$ - 118.4 ° (*c* 1.0, acetone).

***Tetra*-Acetate (209).**



206 **207** **209**

Tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol) was added, in one portion, to a magnetically stirred solution of compound **206** (860 mg, 2.68 mmol) and compound **207** (1.15 g, 3.22 mmol) in 1,4-dioxane (50 mL) under a nitrogen atmosphere at 60 °C for 8 h. The resulting dark-brown reaction mixture was cooled, then diluted with water (100 mL) and EtOAc (200 mL). The separated aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black solid. This material was treated with dry pyridine (20 mL) and acetic anhydride (5 mL, 53 mmol) and the resulting reaction mixture stirred at 18 °C for 16 h, then concentrated under reduced pressure. The residue was subjected to high vacuum (10^{-3} Torr) for 1 h then to flash chromatography (1:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f0.3) then gave a white solid. Recrystallization (hexane/Et_2O) of this material afforded compound **209** (1.10 g, 74% from **206**) as colourless prisms, m.p. 204-206 °C.

^{1}H NMR (300 MHz) δ: 6.18 (2H, d, *J* = 3.0 Hz), 5.72 (2H, d, *J* = 3.0 Hz), 4.89 (2H, dd, *J* = 4.7 and 3.0 Hz), 2.49 (2H, dd, *J* = 12.5 and 3.0 Hz), 2.10 (2H, partially obscured dd), 2.09 (6H, s), 2.07 (6H, s).

^{13}C NMR (75.4 MHz) δ: 170.9 (2xC), 168.8 (2xC), 138.5 (2xC), 124.8 (2xCH), 68.9 (2xCH), 65.9 (2xC), 64.3 (2xCH), 30.8 (2xCH or 2xCH_3), 30.4 (2xCH or 2xCH_3), 21.2 (2xCH or 2xCH_3), 21.0 (2xCH or 2xCH_3).

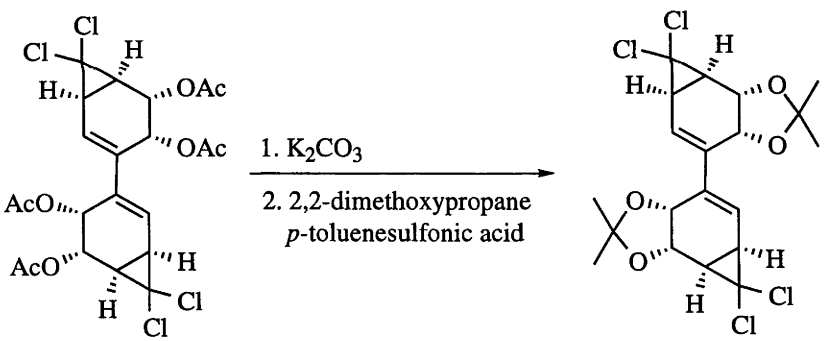
IR ν_{max} 1745 ,1740, 1370, 1245, 1220, 770 cm^{-1}.

EIMS (70eV) *m/z* 558, 556, 554 ($M^{+\cdot}$, 0.3, 0.5, 0.1), 454 (10), 412 (26), 394 (18), 376 (30), 351 (28), 334 (100).

Elemental Analysis Found: C, 47.46; H, 3.80; Cl, 25.50.; $C_{22}H_{22}Cl_4O_8$ requires: C, 47.51; H, 3.99; Cl, 25.50%.

Optical Rotation $[\alpha]_D^{20}$ - 235.0 ° (*c* 1.5, $CHCl_3$).

***Bis*-Acetonide (204).**



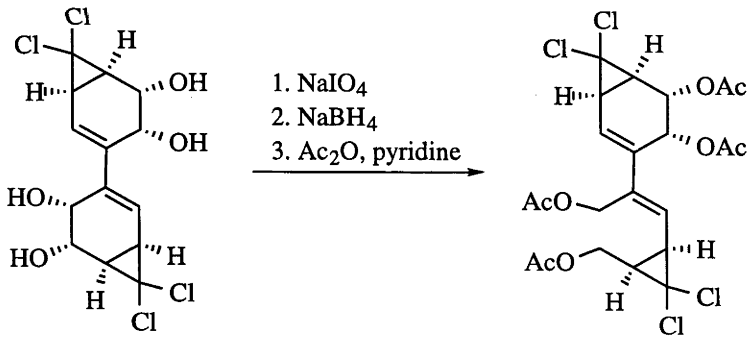
209 **204**

Potassium carbonate (835 mg, 6.04 mmol) was added, in one portion, to a magnetically stirred solution of compound **209** (50 mg, 0.091 mmol) in MeOH (5 mL) maintained at 18 °C under a nitrogen atmosphere. The reaction mixture was heated at reflux for 16 h then concentrated under reduced pressure and the residue partitioned between EtOAc (15 mL) and water (5 mL). The separated aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound **208** (30 mg, 88%) as a

clear, colourless oil. This intractable material was used, without purification, in the next step of the reaction sequence.

p-Toluenesulfonic acid monohydrate (20 mg, 0.08 mmol) was added, in one portion, to a magnetically stirred solution of compound **208** (30 mg, 0.13 mmol) in 2,2-dimethoxypropane (1 mL, 8.1 mmol) maintained at *ca.* -10 °C (salt-ice bath) under a nitrogen atmosphere. After 0.5 h the reaction mixture was diluted with triethylamine (0.5 mL) and concentrated under reduced pressure. The residue was partitioned between Et_2O (10 mL) and water (3 mL) and the separated aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give compound **204** (34 mg, 98%) as a white solid, m.p. 209-210 °C. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **204** produced under the conditions defined earlier (see page 171).

***Tetra*-Acetate (210).**



208 **210**

A solution of sodium metaperiodate (83 mg, 0.39 mmol) in THF/water (2 mL of a 1:1 v/v mixture) was added, dropwise, to a magnetically stirred mixture of compound **208** (50 mg, 0.13 mmol) in THF/water (2 mL of a 1:1 v/v mixture) maintained at 5 °C (ice-bath). After 1 h the reaction mixture was diluted with water (2 mL) and Et_2O (20 mL) and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under

reduced pressure to give a clear, colourless oil (40 mg, 80%). This material was used, without purification, in the next step of the reaction sequence.

Sodium borohydride (88 mg, 2.28 mmol) was added, in small portions, to a magnetically stirred solution of the material obtained as described above (40 mg, 0.10 mmol) in THF/MeOH (2 mL of a 10:1 v/v mixture) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After stirring at 18 °C for 8 h, the reaction mixture was quenched with water (10 mL) and EtOAc (20 mL). The separated aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. The residue was treated with dry pyridine (8 mL) and acetic anhydride (4 mL, 16.8 mmol) and the reaction mixture stirred at 18 °C. After 16 h the reaction mixture was concentrated under reduced pressure. The residue was subjected to high vacuum (10^{-3} Torr) for 1 h then to flash chromatography (2:1 Et_2O/hexane elution). Concentration of the appropriate fractions (R_f 0.4) afforded compound **210** (35 mg, 50% from **208**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.15 (1H, d, J = 3.1 Hz), 5.73 (1H, d, J = 3.1 Hz), 5.60 (1H, d, J = 14.0 Hz), 4.98-4.92 (2H, m), 4.83 (1H, d, J = 12.2 Hz), 4.20 (1H, dd, J = 7.8 and 7.2 Hz), 4.07 (1H, dd, J = 7.8 and 7.2 Hz), 2.72-2.67 (1H, m), 2.52 (1H, dd, J = 10.5 and 3.1 Hz), 2.26 (1H, ddd, J = 7.8, 7.2 and 7.2 Hz), 2.15-2.10 (1H, m), 2.08 (6H, s), 2.05 (6H, s).

^{13}C NMR (75.4 MHz) δ: 171.1 (C), 170.8 (C), 170.6 (C), 169.9 (C), 140.1 (C), 138.6 (C), 124.7 (CH), 124.4 (CH), 68.8 (CH), 66.1 (C), 64.5 (CH), 64.1 (C), 60.8 (CH_2), 60.2 (CH_2), 33.9 (CH), 31.9 (CH), 30.8 (CH), 30.4 (CH), 21.2 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 20.9 (CH_3).

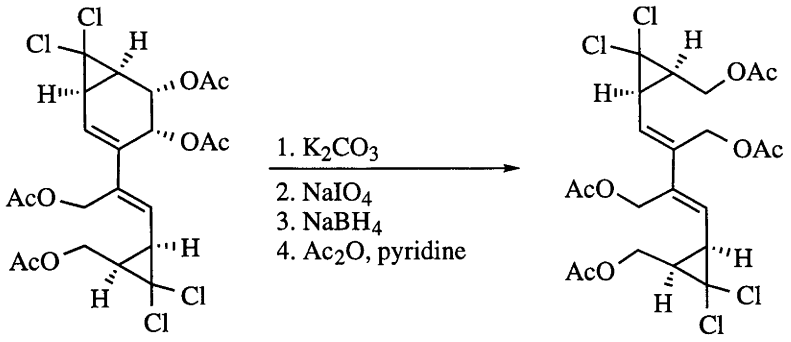
IR ν_{max} 2980 ,1780, 1370, 1245, 1220, 770 cm^{-1}.

EIMS (70eV) *m/z* 558, 556 ($M^{+\cdot}$, 0.2, 0.2), 523, 521 [$(M\text{-}Cl\cdot)^+$, 0.4, 0.4], 396 (9), 359 (60), 299 (100), 281 (78), 263 (64).

HRMS Found $M^{+\cdot}$, 556.0248. $C_{22}H_{24}{}^{35}Cl_4O_8$ requires $M^{+\cdot}$, 556.0225.

Optical Rotation $[\alpha]_D^{20}$ - 75.0 ° (*c* 1.0, $CHCl_3$).

***Tetra*-Acetate (211).**



210 **211**

Potassium carbonate (200 mg, 1.50 mmol) was added to a magnetically stirred solution of compound **210** (16 mg, 0.085 mmol) in anhydrous MeOH (3 mL) maintained at 18 °C under a nitrogen atmosphere. The resulting mixture was heated at reflux for 16 h then cooled and concentrated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and water (5 mL) and the separated aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide a clear, colourless oil (28 mg, 85%). This material was used, without purification, in the next step of the reaction sequence.

A solution of sodium metaperiodate (83 mg, 0.39 mmol) in THF/water (2 mL of a 1:1 v/v mixture) was added to a magnetically stirred solution of the material obtained as described immediately above (14 mg, 0.04 mmol) in THF/water (2 mL, 1:1) maintained at 5 °C (ice-bath). After 1 h the reaction mixture was diluted with water (2 mL) and Et_2O (20 mL) and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil (10 mg, 72%). This material was used, without purification, in the next step of the reaction sequence.

Sodium borohydride (10 mg, 0.25 mmol) was added, in small portions, to a magnetically stirred solution of the material obtained as described immediately above (10 mg, 0.03 mmol) in THF/MeOH (1 mL of a 10:1 v/v mixture) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After stirring at 18 °C for 8 h, the reaction

mixture was quenched with water (10 mL) and EtOAc (20 mL) and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. The residue thus obtained was treated with dry pyridine (10 mL) and acetic anhydride (5 mL, 21 mmol) and the resulting mixture stirred at 18 °C. After 16 h the reaction mixture was concentrated under reduced pressure, and the residue was subjected to high vacuum (10^{-3} Torr) for 1 h then to flash chromatography (2:1 Et_2O/hexane elution). Concentration of the appropriate fractions (R_f 0.4) then gave compound **211** (10 mg, 60% from **210**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.59 (2H, d, *J* = 7.8 Hz), 4.86 (4H, s), 4.14 (4H, d, *J* = 7.5 Hz), 2.75 (2H, dd, *J* = 7.8 and 1.6 Hz), 2.29 (2H, ddd, *J* = 7.8, 7.5 and 7.3 Hz), 2.09 (6H, s), 2.06 (6H, s).

^{13}C NMR (75.4 MHz) δ: 171.0 (2xC), 170.9 (2xC), 139.7 (2xC), 124.9 (2xCH), 64.3 (2xC), 60.9 (2xCH_2), 60.5 (2xCH_2), 33.7 (2xCH), 31.8 (2xCH), 21.9 (2xCH_3), 21.8 (2xCH_3).

IR ν_{max} 2958 ,1741, 1442, 1228, 1036, 818 cm^{-1}.

EIMS (70eV) *m/z* 524, 522 (4, 6), 499 [(M-$C_2H_3O_2^{\cdot}$)$^+$, 21, 33], 362 (62), 264 (80).

CIMS (70eV) *m/z* 578 [(M+NH_4)$^+$, 100].

HRMS Found (M-$C_2H_3O_2^{\cdot}$)$^+$, 501.0235. $C_{22}H_{26}{}^{35}Cl_3{}^{37}ClO_8$ requires (M-$C_2H_3O_2^{\cdot}$)$^+$, 501.0219. Found (M-$C_2H_3O_2^{\cdot}$)$^+$, 499.0256. $C_{22}H_{26}{}^{35}Cl_4O_8$ requires (M-$C_2H_3O_2^{\cdot}$)$^+$, 499.0248.

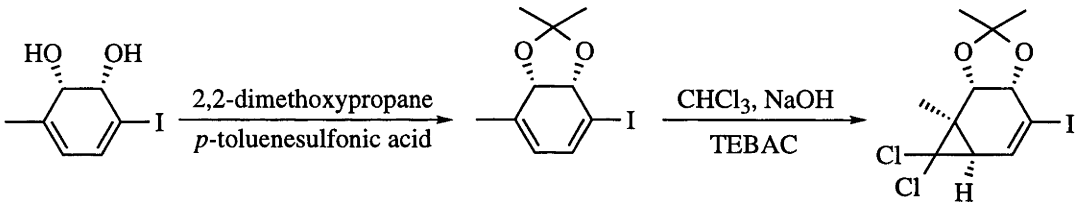
Optical Rotation $[\alpha]_D^{20}$ - 99.0 ° (*c* 1.2, $CHCl_3$).

General Procedure for the Extraction of (1*S*,2*R*)-*cis*-3-Iodo-5-methyl-3,5-cyclohexadiene-1,2-diol (16) from the Fermentation Broth Supplied by Genencor International Inc.

Celite™ (*ca.* 200 g) and cellulose powder (*ca.* 200 g) were added to the fermentation broth containing compound **16** (*ca.* 5 litres). The resulting mixture was stirred at 18 °C for 0.5 h, then filtered. The filtrate was concentrated under reduced pressure (water

bath temperature less than 40 °C) to *ca.* 750 mL then diluted with EtOAc (1.5 litres). The separated aqueous layer was extracted with EtOAc (4 x 500 mL), and the combined organic phases were washed with water (1 x 200 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow solid (64 g) which was comprised primarily of the title compound **16**.

(3a*R*,5a*R*,6a*S*,6b*S*)-6,6-Dichloro-4-iodo-2,2,6a-trimethyl-3a,5a,6a,6b-tetrahydro-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (216).



16 **217** **216**

p-Toluenesulfonic acid monohydrate (210 mg, 1.6 mmol) was added, in one portion, to a magnetically stirred solution of (1*S*,2*S*)-*cis*-3-iodo-5-methyl-3,5-cyclohexadiene-1,2-diol (**16**) (2.0 g, 8.0 mmol) in 2,2-dimethoxypropane (5 mL, 41 mmol) maintained at *ca.* -10 °C (salt-ice bath) under a nitrogen atmosphere. After 0.5 h the reaction mixture was diluted with triethylamine (1.0 mL) then concentrated under reduced pressure. The residue was partitioned between Et_2O (100 mL) and water (50 mL), and the separated aqueous phase extracted with Et_2O (2 x 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide compound **217** (2.04 g, 97%) as a pale-orange oil. This material was used, without purification, in the next step of the reaction sequence.

Sodium hydroxide (13.7 mL of a 50% w/w aqueous solution, 0.17 mol) was added, dropwise, to a magnetically stirred solution of compound **217** (3.09 g, 10.5 mmol) and benzyltriethylammonium chloride (50 mg, 0.22 mmol) in $CHCl_3$ (14.3 mL, 180 mmol) maintained at 5 °C (ice-bath). The resulting dark-brown reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (200 mL) and water (100 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the

combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (20:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.4) a white solid. Recrystallization (hexane) of this material then gave compound **216** (3.0 g, 77%) as colourless needles, m.p. 49-50 °C.

^{1}H NMR (300 MHz) δ: 6.64 (1H, d, *J* = 7.0 Hz), 4.44 (1H, d, *J* = 7.2 Hz), 4.35 (1H, d, *J* = 7.2 Hz), 1.85 (1H, d, *J* = 7.0 Hz), 1.54 (3H, s), 1.43 (s, 3H), 1.40 (3H, s).

^{13}C NMR (75.4 MHz) δ: 132.6 (CH), 109.5 (C), 103.0 (C), 77.4 (CH), 73.7 (CH), 69.2 (C), 37.0 (CH or CH_3), 30.0 (C), 27.9 (CH or CH_3), 26.4 (CH or CH_3), 20.0 (CH or CH_3).

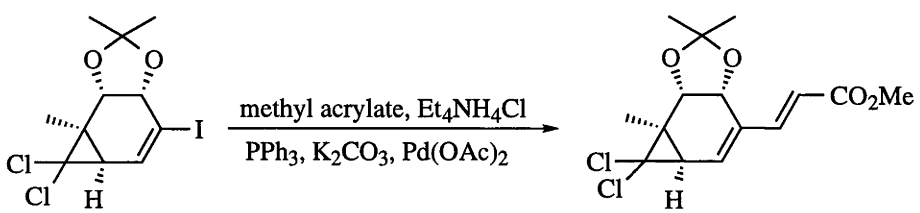
IR ν_{max} 2985 ,2930, 2853, 2360, 1538, 1455, 1374, 1235, 1162, 1021, 918, 877 cm^{-1}.

EIMS (70eV) *m/z* 376, 374 ($M^{+\cdot}$, 52), 361, 359 [$(M\text{-}H_3C\cdot)^+$, 23, 15], 339 (8), 316 (28), 281 (53), 189 (100), 125 (95).

Elemental Analysis Found: C, 35.32; H, 3.31; Cl, 18.69; I, 33.75.; $C_{11}H_{13}Cl_2IO_2$ requires: C, 35.23; H, 3.49; Cl, 18.91; I, 33.84%.

Optical Rotation $[\alpha]_D^{20}$ - 0.95 ° (*c* 1.0, $CHCl_3$).

Ester (218).



216 **218**

Methyl acrylate (73 μl, 0.80 mmol) was added, dropwise, to a magnetically stirred mixture of compound **216** (250 mg, 0.67 mmol), palladium acetate (21 mg, 0.094 mmol), triphenylphosphine (38 mg, 0.15 mmol), potassium carbonate (185 mg, 1.34

mmol) and tetraethylammonium chloride (117 mg, 0.71 mmol) in dry DMF (4 mL) maintained at 18 °C under a nitrogen atmosphere. The reaction mixture was then heated at 75 °C for 16 h, cooled and diluted with water (20 mL) and Et_2O (100 mL). The separated aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to flash chromatography (2:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.5) a white solid. Recrystallization (hexane) of this material then gave compound **218** (174 mg, 78%) as colourless needles, m.p. 69-70 °C.

^{1}H NMR (300 MHz) δ: 7.22 (1H, d, *J* = 16.0 Hz), 6.30 (1H, d, *J* = 16.0 Hz), 6.28 (1H, d, *J* = 6.6 Hz), 4.64 (1H, d, *J* = 6.8 Hz), 4.48 (1H, d, *J* = 6.8 Hz), 3.76 (3H, s), 2.04 (1H, d, *J* = 6.6 Hz), 1.57 (3H, s), 1.39 (3H, s), 1.29 (3H, s).

^{13}C NMR (75.4 MHz) δ: 168.0 (C), 143.7 (CH), 135.0 (C), 130.2 (CH), 120.5 (CH), 109.4 (C), 73.3 (CH), 72.1 (CH), 51.9 (CH_3), 44.8 (C), 34.9 (CH or CH_3), 31.4 (C), 27.7 (CH or CH_3), 26.2 (CH or CH_3), 19.6 (CH or CH_3).

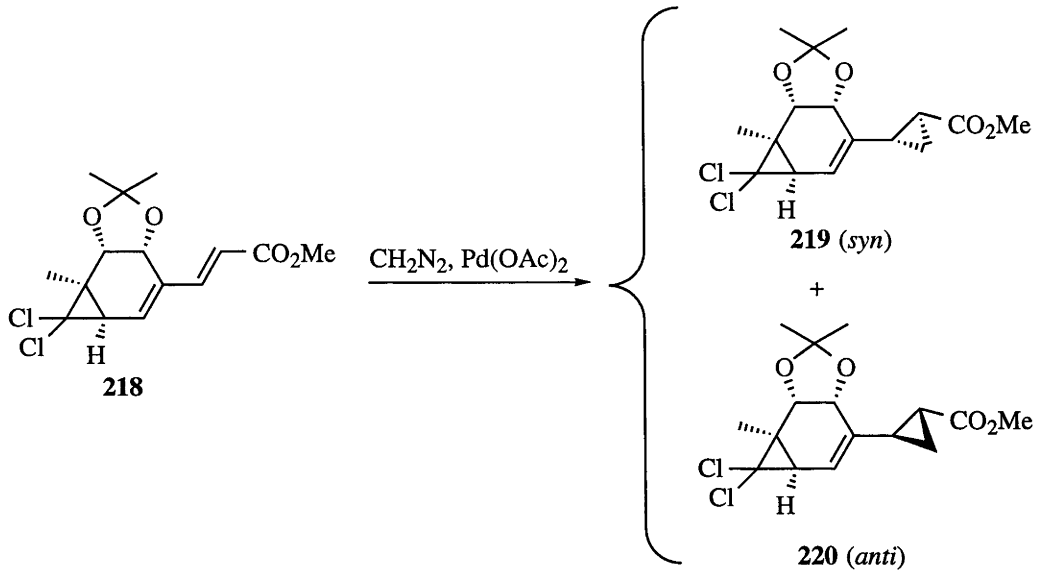
IR ν_{max} 2995 , 1705, 1635, 1295, 1235, 1055 cm^{-1}.

EIMS (70eV) *m/z* 334, 332 ($M^{+\cdot}$, 5, 3), 319, 317 [$(M\text{-}H_3C\cdot)^+$, 10, 7], 300 (8), 274 {$[M\text{-}(CH_3)_2CO]^{+\cdot}$, 39}, 239 (84), 214 (82), 179 (100).

Elemental Analysis Found: C, 53.75; H, 5.40; Cl, 21.29.; $C_{15}H_{18}Cl_2O_4$ requires: C, 54.07; H, 5.44; Cl, 21.28%.

Optical Rotation $[\alpha]_D^{20}$ + 32.3 ° (*c* 1.0, $CHCl_3$).

***Bis*-Cyclopropanes (219 and 220).**



A magnetically stirred solution of compound **218** (29 mg, 0.09 mmol) and palladium acetate (3 mg, 0.01 mmol) in dry CH_2Cl_2 (1 mL) maintained at 5 °C (ice-bath) was treated with an ethereal solution of diazomethane (excess). After 1 h the by now dark-brown reaction mixture was filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to give a pale-yellow oil and this material was subjected to flash chromatography (2:1 hexane/Et_2O). Concentration of the appropriate fractions (R_f0.5) gave a *ca.* 2.3:1 mixture (as determined by GC analysis) of compounds **219** and **220** (27 mg, 86%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.61 (1H, d, J = 6.1 Hz), 4.41 (1H, d, J = 6.6 Hz), 4.36 (1H, d, J = 6.6 Hz), 3.68 (3H, s, minor), 3.69 (3H, s, major), 2.24-2.19 (1H, m), 2.19-2.09 (1H, m), 1.86 (1H, d, J = 6.1 Hz), 1.60-1.53 (1H, m), 1.53 (3H, s), 1.37 (6H, s), 1.28-1.21 (2H, m), 1.05-0.96 (1H, m, minor).

^{13}C NMR (75.4 MHz) δ: 174.2 (C), 137.4 (C), 116.5 (CH), 116.2 (CH), 109.2 (C), 74.6 (CH), 74.4 (CH), 73.2 (CH), 73.1 (CH), 52.2 (CH_3), 33.7 (CH or CH_3), 29.7 (C), 29.6 (CH or CH_3), 27.9 (CH or CH_3), 27.9 (CH or CH_3), 26.4 (CH or CH_3), 26.3 (CH or CH_3), 24.5 (CH or CH_3), 24.3 (CH or CH_3), 22.2 (CH or CH_3), 21.4 (CH or CH_3), 19.5 (CH or CH_3), 19.4 (C), 15.5 (C), 15.4 (C).

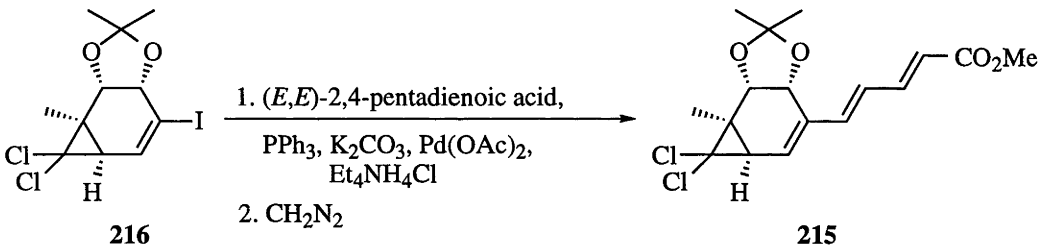
IR ν_{max} 2987 ,2935, 1730, 1438, 1381, 1370, 1056 cm^{-1}.

EIMS (70eV) *m/z* 348, 346 ($M^{+\cdot}$, 0.5, 0.7), 333, 331 [$(M-H_3C\cdot)^+$, 1.7, 2.5], 253 (100), 193 (50), 165 (58), 129 (49).

HRMS Found $M^{+\cdot}$, 348.0694 $C_{16}H_{20}{}^{35}Cl^{37}ClO_4$ requires $M^{+\cdot}$, 348.0709. Found $M^{+\cdot}$, 346.0736 $C_{16}H_{20}{}^{35}Cl_2O_4$ requires $M^{+\cdot}$, 346.0738.

Optical Rotation $[\alpha]_D{}^{20}$ - 42.4 ° (*c* 1.7, $CHCl_3$).

Ester (215).



216 **215**

(*E*,*E*)-2,4-Pentadienoic acid[173] (20 mg, 0.20 mmol), palladium acetate (5 mg, 0.024 mmol), triphenylphosphine (9 mg, 0.033 mmol), potassium carbonate (44 mg, 0.31 mmol) and tetraethylammonium chloride (28 mg, 0.17 mmol) were added, in that order, to a magnetically stirred solution of compound **216** (60 mg, 0.16 mmol) in dry DMF (1 mL) maintained at 18 °C under a nitrogen atmosphere. The resulting mixture was heated at 75 °C for 16 h then cooled and diluted with water (3 mL) and sufficient HCl (3% of an aqueous solution) to attain pH of *ca.* 5-6. The mixture was then extracted with Et_2O (2 x 30 mL) and the combined organic phases were washed with sodium diethyldithiocarbamate (1 x 10 mL of a 1% aqueous solution), dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The crude acid thus obtained was dissolved in CH_2Cl_2 (1 mL) and the resulting solution cooled to 0 °C (ice-salt bath) and treated with an ethereal solution of diazomethane (excess). After stirring for 1 h the dark-brown reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to flash chromatography (2:1 Et_2O/hexane elution) which

afforded, after concentration of the appropriate fractions (R_f 0.5), compound **215** (26 mg, 45% from **216**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 7.30 (1H, dd, *J* = 15.0, 3.5 Hz), 6.68 (1H, dd, *J* = 15.0, 3.5 Hz), 6.45 (1H, d, *J* = 15.0 Hz), 6.11 (1H, d, *J* = 6.3 Hz), 5.93 (1H, d, *J* = 15.0 Hz), 4.66 (1H, d, *J* = 6.4 Hz), 4.49 (1H, d, *J* = 6.4 Hz), 3.74 (3H, s), 2.01 (1H, d, *J* = 6.3 Hz), 1.57 (3H, s), 1.40 (3H, s), 1.30 (3H, s).

^{13}C NMR (75.4 MHz) δ: 167.8 (C), 145.6 (CH), 139.8 (CH), 136.0 (C), 129.0 (CH), 126.4 (CH), 121.3 (CH), 109.3 (C), 73.4 (CH), 72.3 (CH), 70.8 (C), 51.8 (CH_3), 35.0 (CH or CH_3), 31.1 (C), 27.7 (CH or CH_3), 26.2 (CH or CH_3), 19.6 (CH or CH_3).

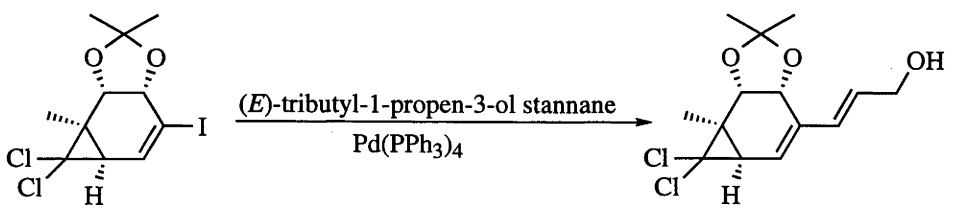
IR ν_{max} 2995 ,1715 ,1610 , 1245, 1140, 1055 cm^{-1}.

EIMS (70eV) *m/z* 360, 358 ($M^{+\cdot}$, 14, 12), 345, 343 [$(M-H_3C\cdot)^+$, 7, 4], 299 [$(M-C_2H_3O_2\cdot)^+$, 29], 284 (37), 265 [$(M-C_6H_7O_2\cdot)^+$, 70], 239 (57), 205 (90), 177 (100).

HRMS Found $M^{+\cdot}$, 360.0708 $C_{17}H_{20}{}^{35}Cl^{37}ClO_4$ requires $M^{+\cdot}$, 360.0709. Found $M^{+\cdot}$, 358.0737 $C_{17}H_{20}{}^{35}Cl_2O_4$ requires $M^{+\cdot}$, 358.0738.

Optical Rotation $[\alpha]_D^{20}$ + 49.6 ° (*c* 2.6, $CHCl_3$).

Alcohol (221).



216 **221**

A solution of (*E*)-tri-*n*-butyl-1-propen-3-ol stannane[176] (6.56 g, 18.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (400 mg, 0.344 mmol) in dry THF (5 mL) was added, dropwise, to a magnetically stirred solution of compound **216** (1.26 g, 3.37 mmol) in dry THF (10 mL) maintained at 18 °C under a nitrogen atmosphere. The reaction mixture was heated at 50 °C for 16 h then cooled and diluted with water (200

mL) and Et_2O (400 mL). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil which was subjected to flash chromatography (2:1 Et_2O/hexane elution). Concentration of the appropriate fractions (R_f 0.4) then gave compound **221** (756 mg, 74%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.17 (2H, s), 5.93 (1H, d, *J* = 6.3 Hz), 4.61 (1H, d, *J* = 6.7 Hz), 4.47 (1H, d, *J* = 6.7 Hz), 4.20 (2H, s), 1.96 (1H, d, *J* = 6.3 Hz), 1.75 (1H, bs), 1.54 (3H, s), 1.39 (3H, s), 1.33 (3H, s).

^{13}C NMR (75.4 MHz) δ: 135.5 (C), 131.0 (CH), 129.9 (CH), 122.2 (CH), 109.1 (C), 73.3 (CH), 72.4 (CH), 70.8 (C), 64.0 (CH_2), 34.6 (CH or CH_3), 30.3 (C), 27.6 (CH or CH_3), 26.0 (CH or CH_3), 19.5 (CH or CH_3).

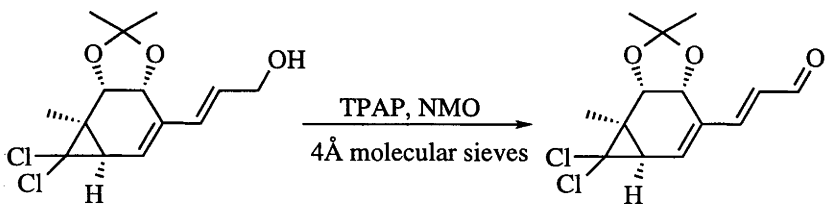
IR ν_{max} 3458 (b), 2983, 2932, 2872, 1380, 1372, 1237, 1022 cm^{-1}.

EIMS (70eV) *m/z* 291, 289 [$(M\text{-}H_3C\cdot)^+$, 3, 2], 248, 246 [$(M\text{-}C_3H_6O\cdot)^+$, 13], 215 (100), 193 (22), 139 (56).

HRMS Found $(M\text{-}H_3C\cdot)^+$, 289.0398 $C_{14}H_{18}{}^{35}Cl_2O_3$ requires $(M\text{-}H_3C\cdot)^+$, 289.0398.

Optical Rotation $[\alpha]_D^{20}$ - 1.47 ° (*c* 1.7, $CHCl_3$).

Aldehyde (222).



221 **222**

A solution of 4-methylmorpholine *N*-oxide (278 mg, 2.28 mmol) in dry CH_2Cl_2 (2 mL) was added, dropwise, to a magnetically stirred mixture of compound **221** (361 mg, 1.19 mmol), 4Å molecular sieves (760 mg) and *tetra-iso*-propylammonium perruthenate (VII) (27 mg, 0.07 mmol) in dry CH_2Cl_2 (4 mL) maintained at 18 °C. After 2 h the reaction mixture was diluted with CH_2Cl_2 (5 mL) then filtered through a

short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (2:1 hexane/Et_2O elution). Concentration of the appropriate fractions (R_f 0.4) then gave compound **222** (263 mg, 74%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 9.54 (1H, d, *J* = 7.7 Hz), 7.00 (1H, d, *J* = 15.9 Hz), 6.54 (1H, dd, *J* = 15.9 and 7.7 Hz), 6.40 (1H, d, *J* = 6.2 Hz), 4.65 (1H, d, *J* = 6.8 Hz), 4.50 (1H, d, *J* = 6.8 Hz), 2.09 (1H, d, *J* = 6.2 Hz), 1.58 (3H, s), 1.37 (3H, s), 1.28 (3H, s).

^{13}C NMR (75.4 MHz) δ: 194.6 (CH), 151.3 (CH), 135.2 (C), 131.7 (CH), 131.3 (CH), 109.6 (C), 73.2 (CH), 72.0 (CH), 70.4 (C), 35.1 (CH or CH_3), 31.6 (C), 27.7 (CH or CH_3), 26.0 (CH or CH_3), 19.5 (CH or CH_3).

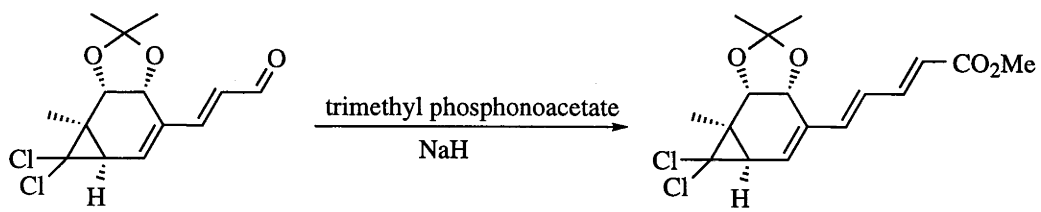
IR ν_{max} 2981, 2897, 1672, 1634, 1605, 1258 cm^{-1}.

EIMS (70eV) *m/z* 289, 287 [$(M-H_3C\cdot)^+$, 6, 9], 246, 244 [$(M-C_3H_6O\cdot)^+$, 21], 215 (100), 181 (73), 145 (75), 115 (64).

HRMS Found $(M-H_3C\cdot)^+$, 289.0218 $C_{14}H_{16}{}^{35}Cl^{37}ClO_3$ requires $(M-H_3C\cdot)^+$, 289.0212. Found $(M-H_3C\cdot)^+$, 287.0246 $C_{14}H_{16}{}^{35}Cl_2O_3$ requires $(M-H_3C\cdot)^+$, 287.0241.

Optical Rotation $[\alpha]_D{}^{20}$ - 4.0 ° (*c* 3.0, $CHCl_3$).

Ester (215).

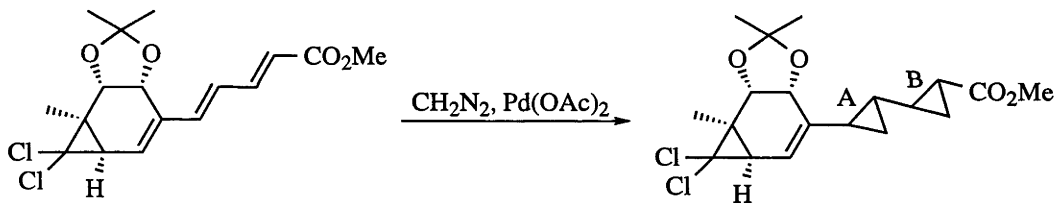


222 **215**

Trimethyl phosphonoacetate (213 μL, 1.32 mmol) was added, dropwise, to a magnetically stirred suspension of sodium hydride (54 mg of a 60% dispersion in mineral oil, 1.34 mmol) (which was freed of oil by washing several times in anhydrous

hexane) in dry THF (8 mL) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After stirring the resulting mixture for 0.3 h a solution of compound **222** (265 mg, 0.88 mmol) in dry THF (2 mL) was added dropwise. The reaction mixture was then stirred at 18 °C for 2 h then diluted with water (20 mL) and Et_2O (100 mL). The separated aqueous phase was extracted with Et_2O (1 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), compound **215** (261 mg, 83%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those derived from an authentic sample of compound **215** produced under the conditions defined earlier (see page 187).

Tri-Cyclopropanes (223-224).



215

223 (A=*syn*, B=*syn*)
224 (A=*syn*, B=*anti*)
225 (A=*anti*, B=*syn*)
226 (A=*anti*, B=*anti*)

A magnetically stirred solution of compound **215** (26 mg, 0.07 mmol) and palladium acetate (3 mg, 0.01 mmol) in dry CH_2Cl_2 (1 mL) maintained at 5 °C (ice-bath) was treated with an ethereal solution of diazomethane (excess). After 1 h the dark-brown reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate was then concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to flash chromatography (2:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a *ca.* 4:3:1:1 mixture (as determined by GC analysis) of compounds **223-226** (27 mg, 86%) as a clear, colourless oil.

Subjection of this material to semi-preparative HPLC (μ-Porosil™ column, 10:1 hexane:*tert*-butyl methyl ether elution, flow rate = 2 mL/min) afforded two fractions, A and B.

Concentration of fraction A (R_t 13.5 min) yielded a mixture of three *diastereomers* of compounds **223-226** (14 mg, 54%), which was used in the next step of the reaction sequence without further purification.

Concentration of fraction B (R_t 15.3 min) yielded one of the single *diastereomers* **223-226** (5 mg, 19%).

^{1}H NMR (300 MHz) δ: 5.42 (1H, d, *J* = 6.3 Hz), 4.42 (1H, d, *J* = 6.6 Hz), 4.39 (1H, d, *J* = 6.6 Hz), 3.66 (3H, s), 1.83 (1H, d, *J* = 6.3 Hz), 1.56 (3H, s), 1.55-1.32 (3H, m), 1.39 (6H, s), 1.12-1.06 (2H, m), 0.77-0.71 (1H, m), 0.56-0.50 (2H, m).

^{13}C NMR (75.4 MHz) δ: 174.4 (C), 139.8 (C), 113.5 (CH), 109.0 (C), 75.0 (CH), 73.2 (CH), 70.6 (C), 52.0 (CH_3), 33.8 (CH or CH_3), 29.4 (C), 28.0 (CH or CH_3), 26.4 (CH or CH_3), 24.4 (CH or CH_3), 21.7 (CH or CH_3), 19.9 (CH or CH_3), 19.5 (CH or CH_3), 19.4 (CH or CH_3), 13.5 (CH_2), 11.5 (CH_2).

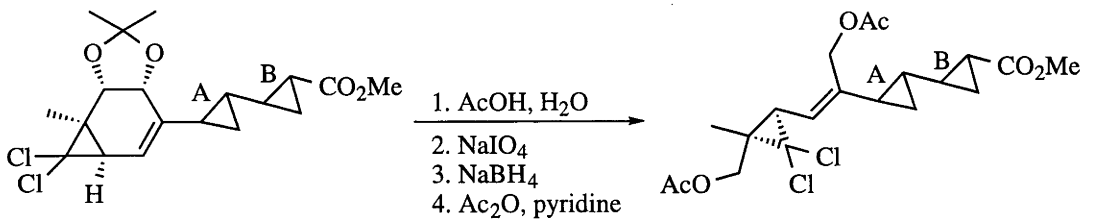
IR ν_{max} 2996, 1729, 1437, 1401, 1208, 1170 cm^{-1}.

EIMS (70eV) *m/z* 388, 386 ($M^{+\cdot}$, 1.0, 1.3), 373, 371 [$(M-H_3C\cdot)^+$, 3.5, 5.6], 293 (85), 215 (96), 167 (72), 139 (100).

HRMS Found $M^{+\cdot}$, 388.1028 $C_{19}H_{24}{}^{35}Cl^{37}ClO_4$ requires $M^{+\cdot}$, 388.1022. Found $(M)^{+\cdot}$, 386.1057 $C_{19}H_{24}{}^{35}Cl_2O_4$ requires $(M)^{+\cdot}$, 386.1051.

Optical Rotation $[\alpha]_D{}^{20}$ + 69.1 ° (*c* 0.5, $CHCl_3$).

Tri-Cyclopropanes (213 and 234-236).



223 (A=*syn*, B=*syn*)
224 (A=*syn*, B=*anti*)
225 (A=*anti*, B=*syn*)
226 (A=*anti*, B=*anti*)

213 (A=*syn*, B=*syn*)
234 (A=*syn*, B=*anti*)
235 (A=*anti*, B=*syn*)
236 (A=*anti*, B=*anti*)

A magnetically stirred solution (*ca.* 4:3:3:1 mixture) of compounds **223-226** (11 mg, 0.028 mmol) in acetic acid (3 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was then diluted with water (5 mL) and EtOAc (10 mL) and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil (8 mg, 83%). This material was used, without purification, in the next step of the reaction sequence.

A solution of sodium metaperiodate (20 mg, 0.09 mmol) in THF/water (1 mL of a 1:1 v/v mixture) was added, dropwise, to a magnetically stirred solution of the material obtained as described immediately above (8 mg, 0.023 mmol) in THF/water (1 mL of a 1:1 v/v mixture) maintained at 5 °C (ice-bath). After 1 h the reaction mixture was diluted with water (2 mL) and Et_2O (20 mL). The separated aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide a clear, colourless oil (7.5 mg, 95%). This material was used, without purification, in the next step of the reaction sequence.

Sodium borohydride (10 mg, 0.25 mmol) was added, in small portions, to a magnetically stirred solution of the material obtained as described immediately above (5 mg, 0.015 mmol) in THF/MeOH (1 mL of a 10:1 v/v mixture) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After stirring at 18 °C for 8 h, the reaction mixture was diluted with water (10 mL) and EtOAc (20 mL). The separated aqueous phase was

extracted with EtOAc (2 x 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide a clear, colourless oil. The residue thus obtained was treated with dry pyridine (10 mL) and acetic anhydride (2.5 mL, 10 mmol) and the resulting mixture stirred at 18 °C for 16 h, then concentrated under reduced pressure. The residue so produced was subjected to high vacuum (10^{-3} Torr) for 1 h then to flash chromatography (2:1 Et_2O/hexane) which afforded, after concentration of the appropriate fractions (R_f 0.4) compounds **213** and **234-236** (5 mg, 67% from **223-226**) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 5.10 (1H, d, *J* = 7.6 Hz), 4.65-4.58 (2H, m), 4.03-4.01 (4H, m), 3.67 (3H, s), 2.13 (1H, d, *J* = 7.6 Hz), 2.11 (3H, s), 2.09 (3H, s), 1.73-1.62 (2H, m), 1.47 (3H, s, major), 1.34 (3H, s, minor), 1.26 (3H, s, minor), 1.25-1.11 (2H, m), 0.76-0.53 (6H, m).

^{13}C NMR (75.4 MHz) δ: 174.7 (C), 172.8 (C), 171.1 (C), 141.7 (C), 119.4 (CH), 108.1 (C), 65.5 (CH_2), 63.0 (CH_2), 52.1 (CH_3), 51.9 (CH_3), 37.3 (CH or CH_3), 33.8 (C), 28.6 (CH or CH_3), 27.5 (CH or CH_3), 25.7 (CH or CH_3), 24.4 (CH or CH_3), 24.3 (CH or CH_3), 24.2 (CH or CH_3), 22.7 (CH or CH_3), 21.8 (CH or CH_3), 21.7 (CH_2), 21.5 (CH or CH_3), 21.3 (CH or CH_3), 21.2 (CH or CH_3), 21.1 (CH or CH_3), 20.2 (CH or CH_3), 19.6 (CH or CH_3), 19.2 (CH or CH_3), 18.4 (CH or CH_3), 16.3 (CH_2), 15.3 (CH or CH_3), 14.2 (CH_2), 13.5 (CH_2), 11.4 (CH_2), 10.3 (CH_2).

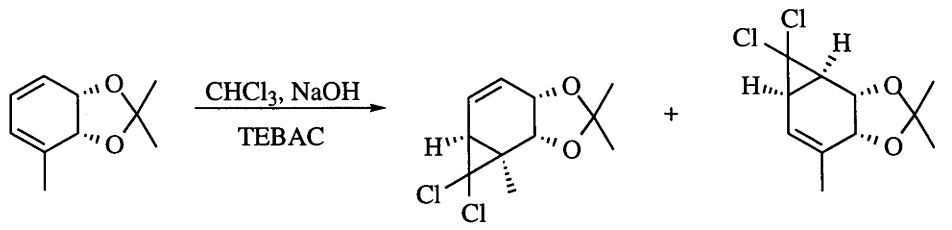
IR ν_{max} 2990, 1732, 1379, 1230, 1171, 1035 cm^{-1}.

EIMS (70eV) *m/z* 240 [$(M\text{-}C_6H_6Cl_2^{\cdot})^+$, 80)], 209 (41), 182 (59), 165 (65), 151 (76).

HRMS Found $(M\text{-}C_6H_6Cl_2^{\cdot})^+$, 240.1366 $C_{19}H_{26}{}^{35}Cl_2O_4$ requires $(M\text{-}C_6H_6Cl_2^{\cdot})^+$, 240.1366.

Optical Rotation $[\alpha]_D{}^{20}$ - 34.2 ° (*c* 1.1, $CHCl_3$).

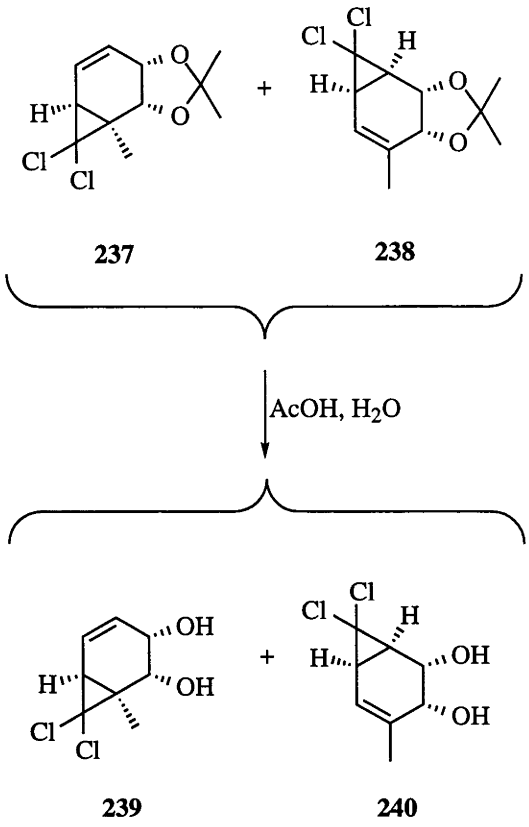
(3a*S*,5a*S*,6a*R*,6b*R*)-6,6-Dichloro-2,2,6a-trimethyl-3a,5a,6a,6b-tetrahydro-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (237) and (3a*R*,5a*R*,6a*R*,6b*S*)-6,6-Dichloro-2,2,4-trimethyl-3a,5a,6a,6b-tetrahydro-5a*H*-cyclopropa[*e*]-1,3-benzodioxole (238).



27 **237** **238**

Sodium hydroxide (4.65 mL of a 50% w/w aqueous solution, 42.2 mmol) was added, dropwise, to a magnetically stirred solution of compound **27** (1.65 g, 9.91 mmol) and benzyltriethylammonium chloride (25 mg, 0.10 mmol) in $CHCl_3$ (5.3 mL, 9.9 mmol) maintained at 5 °C (ice-bath). The resulting dark-brown reaction mixture was stirred vigorously at 18 °C for 16 h then diluted with $CHCl_3$ (100 mL) and water (50 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil. The material obtained this way was subjected to flash chromatography (10:1 hexane/Et_2O elution) which afforded, after concentration of the appropriate fractions (R_f 0.8), a *ca.* 1.2:1 mixture (as determined by ^1H NMR analysis) of compounds **237** and **238** (2.0 g, 82%) as a clear, colourless oil. The spectral data obtained on this material were identical, in all respects, with those previously reported.[75] This material was used, without purification, in the next step of the reaction sequence.

(1*S*,2*R*,3*S*,6*S*)-7,7-Dichloro-1-methylbicyclo[4.1.0]hept-4-ene-2,3-diol (239) and (1*S*,2*S*,3*R*,6*R*)-7,7-Dichloro-4-methylbicyclo[4.1.0]-hept-4-ene-2,3-diol (240).



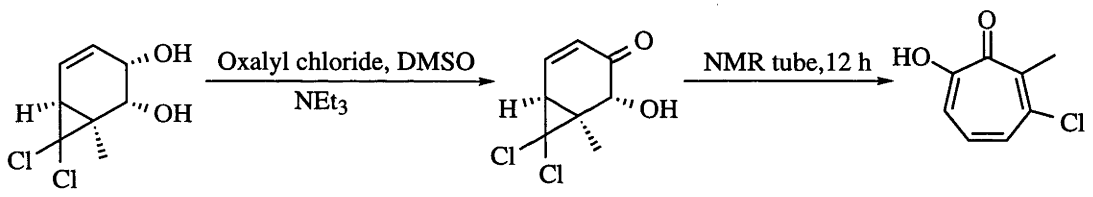
A magnetically stirred solution of compounds **237** and **238** (2.0 g, 8.0 mmol) in acetic acid (55 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was then diluted with water (50 mL) and EtOAc (100 mL), and the separated aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded two fractions, A and B.

Concentration of fraction A afforded, after concentration of the appropriate fractions (R_f0.5) a white solid. Recrystallization (Et_2O) of this material then gave compound **239** (610 mg, 36%) as colourless needles, m.p. 116-117 °C (lit.[75] m.p. 116-117 °C).

The spectral data obtained on this material were identical, in all respects, with those previously reported.[75]

Concentration of fraction B afforded, after concentration of the appropriate fractions (R_f0.4) a white solid. Recrystallization (Et_2O) of this material then gave compound **240** (462 mg, 27%) as colourless needles, m.p. 95-96 °C (lit.[75] m.p. 94-95 °C). The spectral data obtained on this material were identical, in all respects, with those previously reported.[75]

(1*S*,2*R*,6*S*)-7,7-Dichloro-2-hydroxy-1-methylbicyclo[4.1.0]hept-4-en-3-one (242) and 6-Chloro-2-hydroxy-7-methylcyclohepta-2,4,6-trien-1-one (241).



239 **242** **241**

Dimethyl sulfoxide (164 μL, 2.3 mmol) was added, dropwise, to a magnetically stirred solution of oxalyl chloride (94 μL, 1.08 mmol) in dry CH_2Cl_2 (2 mL) maintained at -78 °C (dry-ice/acetone slush bath) under a nitrogen atmosphere. After 0.5 h, a solution of compound **239** (150 mg, 0.72 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. After a further 1.5 h, triethylamine (319 μL, 2.3 mmol) in dry CH_2Cl_2 (2 mL) was added, dropwise, and the reaction mixture was then stirred at -78 °C for 0.25 h and then at -20 °C for 0.1 h before being quenched with water (8 mL). The resulting mixture was poured into Et_2O (50 mL) and the separated organic phase was washed with $KHSO_4$ (2 x 40 mL of a saturated aqueous solution). The combined aqueous layers were extracted with Et_2O (1 x 200 m L) then the combined organic phases were washed with $NaHCO_3$ (2 x 20 mL of a saturated aqueous solution), water (2 x 20 mL) and NaCl (1 x 20 mL of a saturated aqueous solution) before being dried

($MgSO_4$), filtered and concentrated under reduced pressure. The pale-yellow oil obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), compound **242** (156 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.88 (1H, dd, J = 10.1, 5.4 Hz), 6.25 (1H, d, J = 10.1 Hz), 4.40 (1H, s), 2.12 (1H, d, J = 5.4 Hz), 1.53 (3H, s).

IR ν_{max} 3355, 2935, 1670, 1400, 1116 cm^{-1}.

Optical Rotation $[\alpha]_D^{20}$ + 290.0 ° (*c* 1.1, $CHCl_3$).

Upon standing in an NMR tube for 12 h, compound **242** rearranged to give compound **241** as a white solid, m.p. 96-97 °C.

^{1}H NMR (300 MHz) δ: 7.32-7.26 (2H, m), 7.08 (1H, t, J = 11.7 Hz), 6.73 (1H, bs), 2.63 (3H, s).

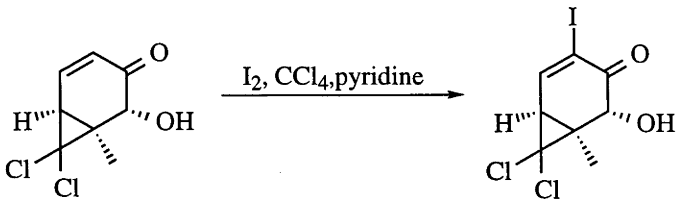
^{13}C NMR (75.4 MHz) δ: 174.2 (C), 165.0 (C), 149.1 (C), 138.6 (C), 132.8 (CH), 130.6 (CH), 117.4 (CH), 20.6 (CH_3).

IR ν_{max} 3355, 2935, 1670, 1400, 1116 cm^{-1}.

EIMS (70eV) *m/z* 172, 170 ($M^{+\cdot}$, 100, 45), 142 [$(M\text{-}CO)^{+\cdot}$, 37], 107 (94), 89 (26), 77 (51).

HRMS Found $M^{+\cdot}$, 172.0104. $C_8H_7{}^{37}ClO_2$ requires $M^{+\cdot}$, 172.0105. Found $(M)^{+\cdot}$, 170.0133. $C_8H_7O_2{}^{35}Cl$ requires $(M)^{+\cdot}$, 170.0134.

(1*S*,2*R*,6*S*)-7,7-Dichloro-4-iodo-2-hydroxy-1-methylbicyclo[4.1.0]-hept-4-en-3-one (243).



242 **243**

A solution of iodine (260 mg, 2.05 mmol) in CCl_4/pyridine (1:1, 2 mL) was added, dropwise, to a magnetically stirred solution of compound **242** (100 mg, 0.485 mmol) in CCl_4/pyridine (1:1, 2 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After stirring at 18 °C for 12 h the by now orange-coloured reaction mixture was diluted with EtOAc (20 mL) and washed with water (2 x 10 mL). The separated organic phase was washed with HCl (1 x 10 mL of a 1M aqueous solution) and $Na_2S_2O_3$ (1 x 10 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.6), compound **243** (103 mg, 64%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 7.62 (1H, d, *J* = 5.6 Hz), 4.53 (1H, s), 3.26 (1H, bs), 2.12 (1H, d, *J* = 5.6 Hz), 1.54 (3H, s).

^{13}C NMR (75.4 MHz) δ: 190.6 (C), 151.0 (CH), 101.1 (C), 71.7 (C), 70.4 (CH), 38.8 (CH or CH_3), 37.5 (C), 17.5 (CH or CH_3).

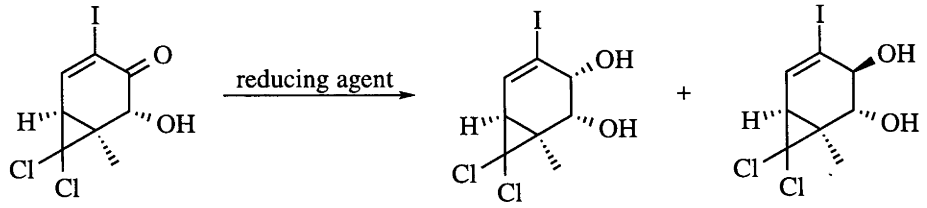
IR ν_{max} 3388, 1680, 1591, 1114, 1091, 1020 cm^{-1}.

EIMS (70eV) *m/z* 336, 334 ($M+2H^+$, 3, 2), 298 (12), 281 (47), 189 (75), 125 (100).

HRMS Found ($M+2H^+$), 337.8960 $C_8H_7O_2{}^{37}Cl_2I$ requires ($M+2H^+$), 337.8965. Found ($M+2H^+$), 335.8985 $C_8H_7{}^{35}Cl{}^{37}ClIO_2$ requires ($M+2H^+$), 335.8994. Found ($M+2H^+$), 333.9015 $C_8H_7{}^{35}Cl_2IO_2$ requires ($M+2H^+$), 333.9024.

Optical Rotation $[\alpha]_D{}^{20}$ + 127.5 ° (*c* 3.2, $CHCl_3$).

(1*S*,2*R*,3*R*,6*S*)-7,7-Dichloro-4-iodo-1-methylbicyclo[4.1.0]hept-4-ene-2,3-diol (244) and (1*S*,2*R*,3*S*,6*S*)-7,7-Dichloro-4-iodo-1-methylbicyclo[4.1.0]hept-4-ene-2,3-diol (245).



243 **244** **245**

Reduction of Compound **243** *with Sodium Borohydride at 5 °C.*

Sodium borohydride (19.5 mg, 0.52 mmol) was added, in small portions, to a magnetically stirred solution of compound **243** (39 mg, 0.12 mmol) and cerium trichloride heptahydrate (193 mg, 0.52 mmol) in MeOH/CH_2Cl_2 (0.5 mL of a 1:1 v/v mixture) maintained at 5 °C (ice-bath) under a nitrogen atmosphere. After stirring at 18 °C for 8 h, the reaction mixture was quenched with water (10 mL) and EtOAc (20 mL). The separated aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), a 36:64 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (39 mg, 98%) as a clear, colourless oil. Subjection of this material to semi-preparative HPLC (μ-Porasil™ column, 95:5 hexane:isopropanol elution, flow rate = 2 mL/min) afforded two fractions, A and B.

Concentration of fraction A (R_t 12.8 min) yielded compound **245** (20 mg, 63%) as a clear, colourless oil.

^1H NMR (300 MHz) δ: 6.43 (1H, m), 4.10 (1H, d, J = 8.6 Hz), 4.06 (1H, d, J = 8.6 Hz), 2.60 (1H, bs), 1.69 (1H, d, J = 3.6 Hz), 1.61 (1H, bs), 1.44 (3H, s).

^{13}C NMR (75.4 MHz) δ: 132.3 (CH), 110.3 (C), 72.7 (CH), 71.4 (CH), 43.9 (C), 39.1 (CH or CH_3), 33.0 (C), 17.2 (CH or CH_3).

IR ν_{max} 3385 ,2979, 2938, 1454, 1404, 1249, 1113 cm^{-1}.

EIMS (70eV) *m/z* 336, 334 ($M^{+\cdot}$, 34), 318, 316 [$(M-H_2O)^{+\cdot}$, 10, 16], 281 (64), 252 (17), 189 (94), 125 (100).

HRMS Found $M^{+\cdot}$, 335.8989 $C_8H_9{}^{35}Cl^{37}ClIO_2$ requires $M^{+\cdot}$, 335.8994. Found $M^{+\cdot}$, 333.9028 $C_8H_9{}^{35}Cl_2IO_2$ requires $M^{+\cdot}$, 333.9024.

Optical Rotation $[\alpha]_D{}^{20}$ + 22.0 ° (*c* 1.0, $CHCl_3$).

Concentration of fraction B (R_t 18.0 min) yielded compound **244** (10 mg, 32%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ: 6.65 (1H, d, *J* = 3.6 Hz), 4.35 (1H, d, *J* = 3.8 Hz), 4.27 (1H, d, *J* = 3.8 Hz), 1.91 (1H, d, *J* = 3.6 Hz), 1.54 (3H, s), (signals due to two -**OH** protons not observed).

^{13}C NMR (75.4 MHz) (d_6 acetone) δ: 135.1 (CH), 103.6 (C), 77.6 (CH), 69.6 (CH), 40.3 (C), 39.6 (CH or CH_3), 31.9 (C), 18.8 (CH or CH_3).

IR ν_{max} 3332 ,2936, 2871, 1455, 1404, 1249, 1113 cm^{-1}.

EIMS (70eV) *m/z* 336, 334 ($M^{+\cdot}$, 4, 3), 318, 316 [$(M-H_2O)^{+\cdot}$, 16, 24], 281 (57), 252 (19), 189 (90), 125 (100).

HRMS Found $M^{+\cdot}$, 335.8983 $C_8H_9{}^{35}Cl^{37}ClIO_2O_2$ requires $M^{+\cdot}$, 335.8994. Found $M^{+\cdot}$, 333.9015 $C_8H_9{}^{35}Cl_2IO_2$ requires $M^{+\cdot}$, 333.9024.

Optical Rotation $[\alpha]_D{}^{20}$ + 54.0 ° (*c* 1.0, $CHCl_3$).

Reduction of Compound **243** *with Sodium Borohydride at -78 °C.*

Sodium borohydride (30 mg, 0.80 mmol) was added, in small portions, to a magnetically stirred solution of compound **243** (60 mg, 0.18 mmol) and cerium trichloride heptahydrate (297 mg, 0.80 mmol) in MeOH/CH_2Cl_2 (1.0 mL of a 1:1 v/v mixture) maintained at -78 °C (dry-ice/acetone slush bath) under a nitrogen atmosphere. After stirring at 18 °C for 8 h, the reaction mixture was quenched with water (10 mL)

and EtOAc (20 mL) and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a 14:86 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (26 mg, 94%) as a clear, colourless oil.

Reduction of Compound **243** *with Zinc Borohydride at -78 °C.*

Zinc borohydride (860 μL of a 0.14 M solution in Et_2O, 0.12 mmol) was added, dropwise, to a magnetically stirred solution of compound **243** (40 mg, 0.12 mmol) in dry CH_2Cl_2 (0.5 mL) maintained at -78 °C (dry-ice/acetone slush bath) under a nitrogen atmosphere. After stirring at -78 °C for 1 h the reaction mixture was quenched with water (10 mL) and EtOAc (20 mL), and the separated aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a 4:96 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (37 mg, 93%) as a clear, colourless oil.

Reduction of Compound **243** *with Lithium Aluminium Hydride at 0 °C.*

A solution of compound **243** (18 mg, 0.053 mmol) in dry THF (0.5 mL) was added, dropwise, to a magnetically stirred solution of lithium aluminium hydride (66 μL of a 1M solution in THF, 0.066 mmol) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was stirred at 18 °C for 6 h then treated, sequentially, with water (1 mL) and sodium hydroxide (1 mL of a 15% aqueous solution). The resulting suspension was filtered and the solids thus retained were washed successively with Et_2O (10 mL) and hot $CHCl_3$ (10 mL). The combined

filtrates were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a 3:97 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (13 mg, 86%) as a clear, colourless oil.

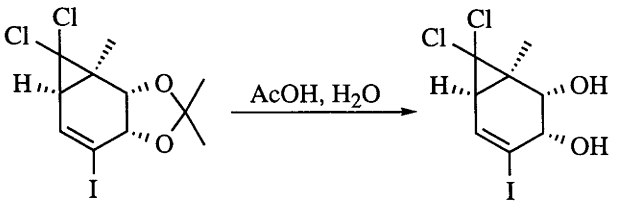
Reduction of Compound **244** *with DIBAL-H at 0 °C.*

DIBAL-H (130 μL of a 1 M solution in THF, 0.13 mmol) was added, dropwise, to a magnetically stirred solution of compound **243** (40 mg, 0.12 mmol) in dry THF (0.5 mL) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. After 2.5 h the reaction mixture was quenched with HCl (5 mL of a 10% aqueous solution) and EtOAc (10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a 37:63 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (36 mg, 92%) as a clear, colourless oil.

Reduction of Compound **243** *with DIBAL-H at -78 °C.*

DIBAL-H (130 μL of a 1 M solution in THF, 0.13 mmol) was added, dropwise, to a magnetically stirred solution of compound **243** (40 mg, 0.12 mmol) in dry THF (0.5 mL) maintained at -78 °C (dry-ice/acetone slush bath) under a nitrogen atmosphere. After 2.5 h the reaction mixture was quenched with HCl (5 mL of a 10% aqueous solution) and EtOAc (10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. The material obtained this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f0.5), a 42:58 mixture (as determined by ^1H NMR analysis) of compounds **244** and **245** (34 mg, 84%) as a clear, colourless oil.

(1*R*,2*S*,3*S*,6*R*)-7,7-Dichloro-4-iodo-1-methylbicyclo[4.1.0]hept-4-ene-2,3-diol (*ent*-244).



216 *ent*-**244**

A magnetically stirred solution of compound **216** (3.57 g, 9.54 mmol) in acetic acid (100 mL of a 60% aqueous solution) was heated at 80 °C for 16 h. The cooled reaction mixture was then diluted with water (200 mL) and EtOAc (300 mL). The separated aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The material obtained in this way was subjected to flash chromatography (2:1 Et_2O/hexane elution) which afforded, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallization ($CHCl_3/Et_2O$) of this material then gave compound *ent*-**244** (2.42 g, 76%) as colourless needles, m.p. 112-113 °C.

^{1}H NMR (300 MHz) δ: 6.65 (1H, d, *J* = 3.6 Hz), 4.35 (1H, d, *J* = 3.8 Hz), 4.27 (1H, d, *J* = 3.8 Hz), 1.91 (1H, d, *J* = 3.6 Hz), 1.54 (3H, s), (signals due to two -**OH** protons not observed).

^{13}C NMR (75.4 MHz) δ (d_6 acetone): 134.7 (CH), 103.6 (C), 77.6 (CH), 69.6 (CH), 40.3 (C), 39.6 (CH or CH_3), 31.9 (C), 18.8 (CH or CH_3).

IR ν_{max} 3332 ,2936, 2871, 1455, 1404, 1249, 1113 cm^{-1}.

EIMS (70eV) *m/z* 336, 334 ($M^{+\cdot}$, 4, 2.5), 318, 316 [$(M-H_2O)^{+\cdot}$, 18, 16], 281 (37), 252 (32), 189 (65), 125 (100).

Elemental Analysis Found: C, 28.75; H, 2.68; Cl, 20.85; I, 37.64.; $C_8H_9Cl_2IO_2$ requires: C, 28.69; H, 2.71; Cl, 21.17; I, 37.89%.

Optical Rotation $[\alpha]_D^{20}$ - 57.2 ° (*c* 3.2, $CHCl_3$).

REFERENCES

1. Lin, H. W.; Walsh , C. T. in "The Chemistry of the Cyclopropyl Group"; Patai, S., Rappoport, Z., Eds; Wiley; 1987; Chapter 16.
2. Suckling, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 537.
3. (a) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679; (b) Still, W. C.; Collum, D.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094; (c) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256; (d) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254.
4. Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807.
5. *Chemical and Engineering News* **1996**, Feb. 19, 24.
6. Yoo, H.-D.; Gerwick, W. H. *J. Nat. Prod.* **1995**, *58*, 1961 and references cited there-in.
7. Blokhin, A. V.; Yoo, H.-D.; Geralds, R. S.; Nagle, D. G.; Gerwick, W. H.; Hamel, E. *Molecular Pharm.* **1995**, *48*, 523.
8. (a) Nagle, D. G.; Gerwick, W. H. *J. Org. Chem.* **1994**, *59*, 7227; (b) Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.* **1990**, *31*, 2995.
9. (a) White, J. D.; Jennies, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224; (b) White, J. D.; Jennies, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970.
10. Baertschi, S. W.; Brash, A. R.; Harris, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 5003.
11. Brash, A. R. *J. Am. Chem. Soc.* **1989**, *111*, 1891.
12. Corey, E. J.; d'Alarcao, M.; Matsuda, S. P. T.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 289.
13. Ringel, S. M.; Greenough, R. C.; Roemer, S.; Conner, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandtman, M. *J. Antibiotics* **1977**, *30*, 371.
14. (a) Kende, A. S.; Mendoza, J. S.; Fujii, Y. *Tetrahedron* **1993**, *49*, 8015; (b) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739; (c) Michelet, V.; Besnier, I.; Genêt, J. P. *Synlett* **1996**, 215.
15. Nishizuka, Y. *Nature (London)* **1988**, *334*, 661.

16. Gustafson, K. R.; Cardellina II, J. H.; McMahon, J. B.; Gulakowski, R. J.; Ishitoya, J.; Szallasi, Z.; Lewin, N. E.; Blumberg, P. M.; Weislow, O. S.; Beutler, J. A.; Buckheit, Jr, R. W.; Cragg, G. M.; Cox, P. A.; Bader, J. P.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 1978.

17. Ire, K.; Ishii, T.; Ohigashi, H.; Wender, P. A.; Miller, B. L.; Takeda, N. *J. Org. Chem.* **1996**, *61*, 2164.

18. Stammer, C. H. *Tetrahedron* **1990**, *46*, 2234.

19. Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.

20. Burgess, K.; Ho, K.-K.; Moye-Sherman D. *Synlett* **1994**, 575.

21. Toniolo, C.; Crisma, M.; Valle, G.; Bonora, G.; Barone, V.; Benedetti, E.; Blasio, B. D.; Pavone, V.; Pedone, C.; Lelj, F. *Pept. Chem.* **1987**, 45.

22. Kimura, H.; Stammer, C. H.; Shimohigashi, Y.; Cui, R.-L.; Stewart, J. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 112.

23. Breckenridge, R. J.; Suckling, C. J. *Tetrahedron* **1986**, *42*, 5665.

24. Sakamura, S.; Ichichara, A.; Shiraishi, K.; Sato, H.; Nishiyama, K.; Sakai, R.; Furusaki, A.; Matsumoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 636.

25. Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103.

26. Arenal, I.; Bernabé, M.; Fernandez-Alvarez, E.; Gibello, A. *Anal. Quim.* **1983**, *79*, 65.

27. Grouiller, A.; Nioche, J. Y.; Barailler, J.; Roche, M.; Pacheco, H. *Eur. J. Med. Chem.* **1980**, *15*, 139.

28. Bernabé, M.; Cuevas, O.; Fernandez-Alvarez, E. *Anal. Quim.* **1979**, *75*, 977.

29. Pages, R.; Burger, A. *J. Med. Chem.* **1966**, *9*, 766.

30. *Classics in Total Synthesis - Targets, Strategies, Methods*, Nicolaou, K. C.; Sorensen, E. J. B.; Kaplan, Ed.; VCM, 1996; Chapter 1.

31. Salaün, J. *Chem Rev.* **1989**, *89*, 1247.

32. Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197.

33. Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

34. Hoveyda, A. H.; Evans, D. A. *Chem Rev.* **1993**, *93*, 1307.

35. (a) Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166; (b) Charette, A. B.; Marcoux, J.-F.; Côté, B. *Tetrahedron Lett.* **1991**, *32*, 7215; (c) Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933; (d) Charette, A. B.; Turcotte, N.; Côté, B. *J. Carbohydr. Chem.* **1994**, *13*, 933; (e) Charette, A. B.; Turcotte, N.; Marcoux, J.-F. *Tetrahedron Lett.* **1994**, *35*, 513; (f) Charette, A. B.; Marcoux, J.-F. *Tetrahedron Lett.* **1993**, *34*, 7157; (g) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592.

36. Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.

37. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

38. Masamune, S.; Lowenthal, R. E.; Abiko, A. *Tetrahedron Lett.* **1990**, *31*, 6005.

39. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

40. Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 3.

41. Denmark, S. E.; Stavenger, R. A.; Faucher, A-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375.

42. Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653.

43. Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E. *Biochemistry* **1968**, *7*, 3795.

44. Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626.

45. Gibson, D. T.; Zylstra, G. J.; Chauhan, S. in *Pseudomonas; Biotransformations, Pathogenesis and evolving Biochemistry*, Silver, S.; Charkraberty, B.; Iglewski, B.; Kaplan, Ed.; Am. Soc. for Microbiol., 1990, Chapter 13, p. 121.

46. Gibson, D. T.; Subramanian, V. in *Microbial Degradation of Organic Compounds*, Gibson, D. T., Ed; Microbiology Series, Vol. 13, Marcel Dekkar: New York, 1984; Chapter 7.

47. Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.* **1998**, 309.

48. Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem* **1989**, *264*, 14940.

49. Hudlicky, T., in ACS symposium Series, Vol 626, Anastas, P. T.; Williamson, T. C., Ed, ACS, Washington, D.C., 1996, p. 180.

50. Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J.; Whited, G.; Seemayer, R. *J. Am. Chem. Soc.* **1994**, *116*, 1147.

51. Boyd, D. R.; Sharma, N. D.; Groocock, M. R.; Kerley, N. A.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun.* **1993**, 974.

52. Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1995**, 117.

53. Berry, A.; Battist, S.; Peck, S.; Power, S.; Weyler, W. *2nd Biomass Conf. Am.*; *Energy, Environ., Agric. Ind.*, National Renewable Energy Laboratory, Golden (USA), 1995, p. 1121.

54. Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larson, R. D.; Verhoven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619.

55. Ballard, D. G. H.; Courtis, A.; Shirley, A.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1983**, 954.

56. Kossmehl, G. A. In *Handbook of Conducting Polymers*; Skotheim, T., Ed.; Marcel Dekker: New York, 1986; Vol 1, Chapter 10.

57. (a) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907; (b) Schrock, R. R. *Acc. Chem. Res.* **1990**, *24*, 158.

58. Conticello, V. P.; Gin, D. L.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 9708.

59. Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

60. Banwell, M. B.; Dupuche, J. R. *J. Chem. Soc., Chem. Commun.* **1996**, 869.

61. Banwell, M. B.; Hockless, D. C. R.; Holman, J. W.; Longmore R. W.; Pham, H. T. T. *Synlett*, to be submitted.

62. (a) Nicolaou, K. C.; Dai, W.-M.; Guy R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15; (b) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Syn.* **1994**, *1*, 47; (c) Guéritte, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160; (d) Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Nat. Prod.* **1993**, *61*, 1; (e) Suffness, N. *Annual Reports in Medicinal Chemistry*, Academic Press, New York, 1993, vol. 28, Chapter 32; (f) Swindell, C. S. *Org. Prep. Proc. Int.* **1993**, *23*, 465.

63. Banwell, M. G.; Darmos, P.; Hockless, D. C. R.; McLeod, M. D. *Synlett.* **1998**, 897.

64. Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Price, J. D. *J. Am. Chem. Soc.* **1990**, *112,* 9439.

65. Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Price, J. D. *Isr. J. Chem.* **1991**, *31,* 229.

66. Hudlicky, T.; Thorpe, A. J. *Synlett* **1994**, 899.

67. Hudlicky, T.; Abboud, K. A.; Entwhistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J. *Synthesis* **1996**, 897.

68. Hudlicky, T.; Abboud, K. A.; Bolonick, J.; Maurya, R.; Stanton, M. L.; Thorpe, A. J. *J. Chem. Soc., Chem. Commun.* **1996**, 1717.

69. Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114,* 9694.

70. Hudlicky, T.; Königsberger, K.; Rouden, J.; Tian, X. *J. Am. Chem. Soc.* **1994**, *116,* 4037.

71. Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.

72. Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. *Synlett* **1990**, 433.

73. Downing, W.; Latouche, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2613.

74. Mahon, M. F.; Molloy, C. A.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O.; Winders, J. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1255.

75. Banwell, M. G.; Collis, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1343.

76. Tran, C. H.; Crout, D. H. G.; Errington, W.; Whited, G. M. *Tetrahedron: Asymmetry* **1996**, *7*, 691.

77. (a) Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1160; (b) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741.

78. Corey, E. J.; Jautelat, M.; Oppolzer, W. *J. Am. Chem. Soc.* **1967**, *89*, 3912.

79. (a) Krief, A.; Dumont, W.; Pasau, P. *Tetrahedron Lett.* **1988**, *29*, 1079; (b) Krief, A.; Dumont, W.; Pasau, P. *Tetrahedron Lett.* **1988**, *29*, 1083.

80. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

81. (a) Pagni, R. M.; Watson, C. R., Jr. *J. Chem. Soc., Chem. Commun.* **1974**, 224; (b) Pagni, R. M.; Watson, C. R., Jr.; Dodd, J. R.; Bloor, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 2551.

82. Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.

83. Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*, Halton, B., Ed.; JAI: Greenwich, CT 1991, Vol. 1, p. 23.

84. Banwell, M. G.; Forman, G. S.; Hockless, D. *Acta Cryst.* **1996**, *C52*, 1804.

85. Dehmlow, E. V. *Liebigs Ann. Chem.* **1972**, *758*, 148.

86. Baird, M. S.; Gerrard, M. E. *Tetrahedron Lett.* **1985**, *26*, 6353.

87. (a) Rigby, J. H.; Bellemin, A.-R. *Synthesis* **1989**, 188; (b) Lipshultz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672; (c) Harayama, T.; Fukushi, H.; Ogawa, K.; Yoneda, F. *Chem. Pharm. Bull.* **1985**, *33*, 3564.

88. Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279.

89. Martel, J. in *The Development and Manufacture of Pyrethroid Insecticides*; Collins, A. N.; Sheldrake, G. N.; Crosby J., Eds; Wiley; 1992 and references cited there-in.

90. (a) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473; (b) Jautelat, M.; Lantzsch, R. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 703.

91. Naumann, K. *Synthetic Pyrethroid Insecticides*; Springer-Verlag; Berlin, 1990.

92. Ariens, E. J.; van Rensen, J. J. S.; Welling, W. *Stereoselectivity of Pesticides, Biological and Chemical Problems*, Elsevier, Amsterdam, 1988.

93. For selected examples see (a) Matsui, M.; Yoshioka, H.; Yamada, Y.; Sakamoto, H.; Kitahara, T. *Agric. Biol. Chem.* **1965**, *29*, 784. (b) Mitra, R. B.; Khanra, A. S. *Synth. Commun.* **1977**, *7*, 245. (c) Fitzsimmons, B. J.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1979**, *101*, 6123.

94. Klescick, W. A.; Reed, M. W.; Bordner, J. *J. Org. Chem.* **1987**, *51*, 3168.

95. Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, *16*, 1707.

96. d`Angelo, J.; Revial, G.; Azerad, R.; Buisson, D. *J. Org.Chem.* **1986**, *51*, 40.

97. De Vos, M. J.; Krief, A. *Tetrahedron Lett.* **1983**, *23*, 103.

98. Meyers, A. I.; Romo, D. *Tetrahedron Lett.* **1989**, *30*, 1745.

99. Tessier, J. R. in *Recent Advances in the Chemistry of Insect Control*; Janes, N.F., Ed; The Royal Society of Chemistry; 1985; p. 26.

100. (a) Mandal, A. K.; Borude, D. P.; Armugasamy, R.; Soni, N. R.; Jawalker, D. G.; Mahajan, S. W.; Ratnam, K. R.; Goghare, A. D. *Tetrahedron* **1986**, *42*, 5715; (b) Bakshi, D.; Mahindroo, V. K.; Soman, R.; Dev, S. *Tetrahedron* **1989**, *45*, 767; (c) Kolesnik, V. D.; Rukavishnikov, A. V.; Tkachev, A. V. *Mendeleev Commun.* **1995**, 179.

101. Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

102. DattaGupta, A.; Singh, R.; Singh, V. *Synlett* **1996**, 69.

103. Hintz, H. L.; Johnson, D. C. *J. Org. Chem.* **1967**, *32*, 556.

104. (a) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, P. *Tetrahedron* **1988**, *44*, 3039; (b) Veyrat, M.; Fantin, L.; Desmoulins, S.; Petitjean, A.; Mazzanti, M.; Ramasseul, R.; Marchon, J.-C.; Bau, R. *Bull. Soc. Chim. Fr.* **1997**, *134*, 703.

105. Banwell, M. G.; Forman, G. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2565.

106. (a) Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157; (b) O'Conner, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075.

107. Lipid Research Clinics Program, *J. Am. Med. Assoc.* **1984**, *251*, 351.

108. Lipid Research Clinics Program, *J. Am. Med. Assoc.* **1984**, *251*, 365.

109. Grundy, S. M. *Cholesterol and Atherosclerosis, Diagnosis and Treatment*, Gower Medical, New York, 1990.

110. Gibbs, J. B. *Cell* **1991**, *65*, 1.

111. Glomset, J. A.; Gelb, M. H.; Farnsworth, C. C. *Trends Biochem. Sci.* **1990**, *15*, 139.

112. Goldstein, J. L.; Brown, M. S. *Nature (London)* **1990**, *343*, 425.

113. Sasiak, K.; Rilling, H. C. *Arch. Biochem. Biophys.* **1988**, *260*, 622.

114. Jennings, S. M.; Tsay, Y. H.; Fisch, T. M.; Robinson, G. W. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 6038.

115. McKenzie, T. L.; Jiang, G.; Straubhaar, J. R.; Conrad, D. G.; Schechter, I. *J. Biol. Chem.* **1992**, *267*, 21368.

116. Schechter, I.; Klinger, E.; Rucker, M. L.; Engstrom, R. G.; Spirito, J. A.; Islam, M. A.; Boettcher, B. R.; Weinstein, D. B. *J. Biol. Chem.* **1992**, *267*, 8628.

117. Keller, R. K.; Cannons, A.; Vilsaint, F.; Zhao, Z.; Ness, G. C. *Arch. Biochem. Biophys.* **1993**, *302*, 304.

118. Robinson, G. W.; Tsay, Y. H.; Kienzle, B. K.; Smith, M. C.; Bishop, R. W. *Mol. Cell Biol.* **1993**, *13*, 2706.

119. M'Baya, B.; Fegueur, M.; Servouse, M.; Karst, F. *Lipids* **1989**, *24*, 1020.

120. Poulter, C. D.; Marsh, L. L.; Hughes, J. M.; Argyle, J. C.; Satterwhite, D. M.; Goodfellow, R. J.; Moesinger, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 3816.

121. Corey, E. J.; Volante, R. P. *J. Am. Chem. Soc.* **1976**, *98*, 1291.

122. Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70.

123. Jarstfer, M. B.; Blagg, B. S. J.; Rogers, D.; Poulter, C. D. *J. Am. Chem. Soc.* **1996**, *118*, 13089.

124. Levy, B. D.; Petasis, N. A.; Serhan, C. N. *Nature (London)* **1997**, *389*, 985.

125. Abe, I.; Tomesch, J. C.; Wattanasin, S.; Prestwich, G. D. *Nat. Prod. Rep.* **1994**, 279, and references cited there-in.

126. Poulter, C. D.; Capson, T. L.; Thompson, M. D.; Bard, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 3734.

127. Capson, T. L.; Thompson, M. D.; Dixit, V. M.; Gaughan, R. G.; Poulter, C. D. *J. Org. Chem.* **1988**, *53*, 5903.

128. Kusano, M.; Abe, I.; Sanakawa, U.; Ebizuka, Y. *Chem. Pharm. Bull.* **1991**, *39*, 239.

129. Abe, I.; Bai, M.; Xiao, X.; Prestwich, G. D. *Biochem. Biophys. Res. Commun.* **1992**, *187*, 32.

130. Moore, W. R.; Schatzman, G. L. *J. Biol. Chem.* **1992**, *267*, 22003.

131. Coates, R. M.; Robinson, W. H. *J. Am. Chem. Soc.* **1971**, *93*, 1785.

132. Altman, L. R.; Kowerski, R. C.; Rilling, H. C. *J. Am. Chem. Soc.* **1971**, *93*, 1782.

133. Campbell, R. V. M.; Crombie, L.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1971**, 218.

134. Altman, L. R.; Kowerski, R. C.; Laungani, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 6174.

135. Rogers, D. H.; Yi, E. C.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 941.

136. Coates, R. M.; Ley, D. A.; Cavender, P. L. *J. Org. Chem.* **1978**, *43*, 4915.

137. van Tamelen, E. E.; Dewey, R. S.; Timmons, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 3725.

138. Hudlicky, T.; Boros, C.; Boros, E. E. *Synthesis* **1992**, 174.

139. Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787.

140. Williamson, K. L.; Lanford, C. A.; Nicholson, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762.

141. Kuwajima, I.; Doi, Y. *Tetrahedron Lett.* **1972**, *12*, 1163.

142. Stothers, J. B. in *Organic Chemistry, Carbon-13 NMR Spectroscopy*; Blomquist, A. T.; Wasserman, H. Ed.; Academic Press: New York, 1972; Vol. 24; p. 80.

143. Crombie, L.; King, R. W.; Whiting, D. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 913.

144. Bohlmann, F.; Zeisberg, R.; Klein, E. *Org. Mag. Res.* **1975**, *7*, 426.

145. de Haan, J. W.; van de Ven, L. J. M. *Org. Mag. Res.* **1973**, *3*, 147.

146. Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1.

147. Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260.

148. Horner, L.; Hoffman, H. M. R.; Wippel, H. G. *Chem Ber.* **1958**, *91*, 61.

149. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chem. Fr.* **1993**, *130*, 856; (b) Bellingham, R.; Jarowicki, K.; Kocienski. P.; Martin, V. *Synthesis* **1996**, 285.

150. Zhang, D.; Poulter, C. D. *Anal. Biochem.* **1993**, *213*, 356.

151. Woolfenden, W. R.; Grant, D. M. *J. Am. Chem. Soc.* **1966**, *88*, 1496.

152. Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

153. Won-Chung, J. K.; Bennett, J. E. *Medical Mycology*; Lee & Febiger: Philidelphia, 1992.

154. Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748.

155. (a) Yoshida, M.; Horikoshi, K. *US Pat.*, 4803074, **1989**; (b) *Chem. Abstr.* **1989**, *110*, 210961e.

156. Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilman, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629.

157. Barrett, G. M.; Kasdorf, K. *J. Chem. Soc., Chem. Commun.* **1996**, 325.

158. Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J. Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096.

159. Lipshultz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815.

160. Walborsky, H. M.; Banks, R. B.; Banks, M. L. A.; Duraisamy, M. *Organometallics* **1982**, *1*, 667.

161. Barton, D. H. R.; Crich, D. C.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.

162. Barrett, A. G.; Hamprecht, D.; White, A. J.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863.

163. Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327.

164. Barrett, A. G.; Hamprecht, D.; White, A. J.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608.

165. Barrett, A. G.; Gross, T.; Hamprecht, D.; Ohkubo, M.; White, A. J.; Williams, D. J. *Synthesis* **1998**, 490.

166. (a) Charette, A.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809; (b) Barrett, A. G. M.; Doubleday, W. W.; Tustin, G. J. *Tetrahedron* **1996**, *52*, 15325; (c) Taylor, R. E.; Ameriks, M.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057; (d) Theberge, C. R.; Verbicky, C.; Zercher, C. K. *J. Org. Chem.* **1996**, *61*, 8792; (e) McDonald, W. S.; Verbicky, C.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 1215; (f) Cebula, R. E. J.; Hanna, M. R.; Verbicky, C.; Zercher, C. K. *Tetrahedron Lett.* **1996**, *37*, 8341; (g) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1995**, *36*, 5495; (h) Itoh, T.; Emoto, S.; Kondo, M. *Tetrahedron* **1998**, *54*, 5225.

167. Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.

168. Entwistle, D. A.; Hudlicky, T. *Tetrahedron Lett.* **1995**, *36*, 2591.

169. (a) Negishi, E.; Takahashi, T.; King, A. O. *Org. Synth.* **1987**, *66*, 67; (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

170. Noheda, P.; García-Ruiz, G.; Pozuelo, M. C.; Abbassi, K.; Pascual-Alfonso, E.; Alonso, J. M.; Jiménez-Barbero, J. *J. Org. Chem.* **1998**, *63*, 6772.

171. Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693.

172. Stille, K. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

173. Fischetti, W.; Mak, K. T.; Stakem, G.; Kim, J.-I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.

174. Mende, U.; Raduchel, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, *9*, 629.

175. Ma, D.; Ma, Z.; Jiang, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889.

176. Wender, P. A.; Seiburth, S.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.

177. Ley, S. V., Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

178. Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386.

179. (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651; (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480; (c) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

180. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. N.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

181. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

182. de Boer, T. J.; Backer, H. J. *Org. Syn., Coll. Vol.* **1963**, *4*, 250.

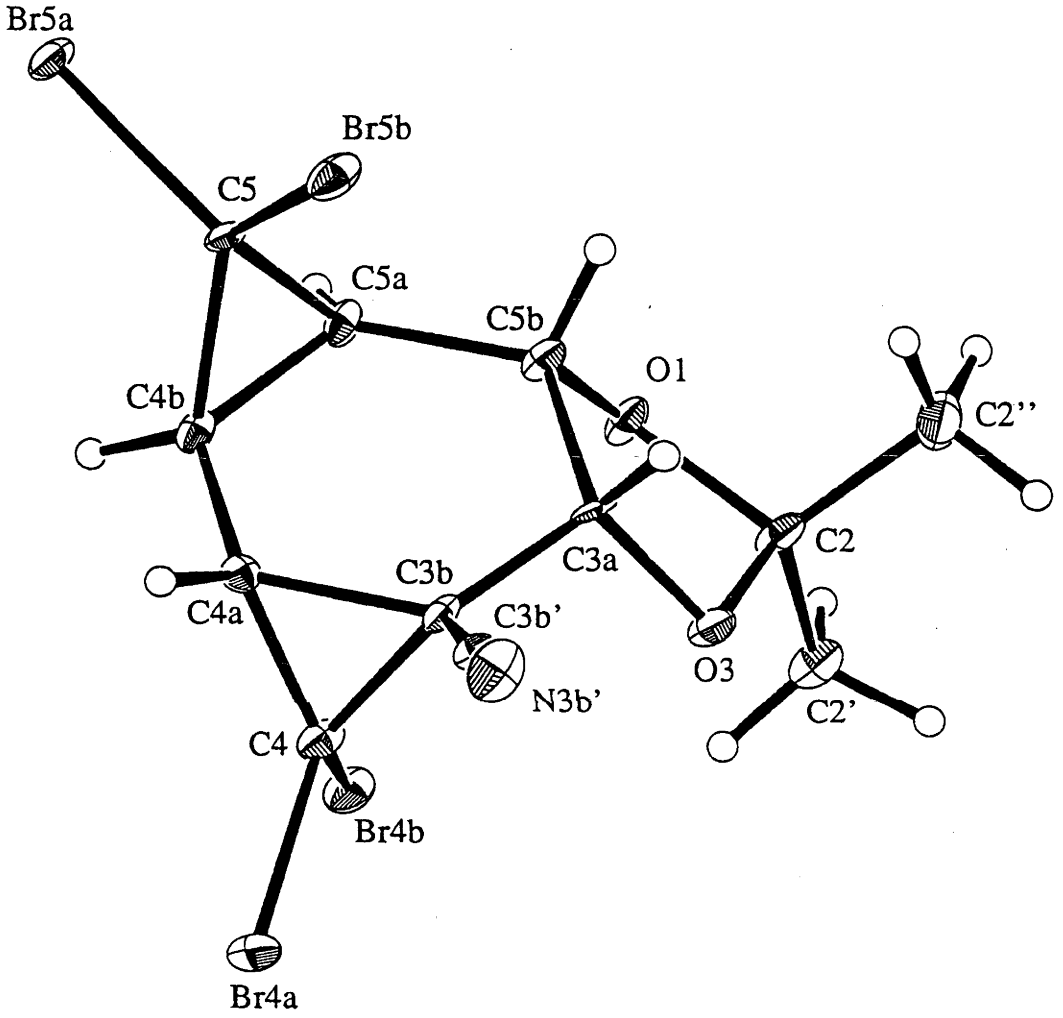
183. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R., *Purification of Laboratory Chemicals*, Pergamon Press, Oxford Press, Oxford, UK, 1988, 3rd Edition.

184. Watson, S. C.; Eastham, J. F. *J. Organometallic Chem.* **1967**, *9*, 165.

APPENDICES

Appendix 1: X-Ray Crystallographic Data

1.1 X-Ray Structure Report for Compound 75*



* X-ray crystal data are presented as provided by Dr. David Hockless (Research School of Chemistry, ANU).

Experimental

Data Collection

A colourless irregular crystal of $C_{12}H_{11}Br_4NO_2$ having approximate dimensions of 0.20 x 0.16 x 0.08 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a 12kW rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $97.83 < 2\theta < 99.86°$ corresponded to a primitive monoclinic cell with dimensions:

$a = 6.322(1)\ \AA$

$b = 13.476(1)\ \AA \qquad \beta = 106.54(1)°$

$c = 9.115(2)\ \AA$

$V = 744.5(2)\ \AA^3$

For Z = 2 and F.W. = 520.84, the calculated density is 2.32 g/cm^3. Based on the systematic absences of:

0k0: $k \neq 2n$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of -60 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.31° with a take-off angle of 6.0°. Scans of $(1.30 + 0.30 \tan \theta)°$ were made at a speed of 32.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 1283 reflections which were collected, 1170 were unique ($R_{int} = 0.062$). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 133.5 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted

in transmission factors ranging from 0.61 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 1.5(3)e-06).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1134 observed reflections ($I > 3.00\sigma(I)$) and 171 variable parameters and converged (largest parameter shift was <0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.027$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.033$$

The standard deviation of an observation of unit weight[4] was 2.80. The weighting scheme was based on counting statistics and included a factor (p = 0.010) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.74 and -0.51 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidori, G. (1994). J. Appl. Cryst., in preparation.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$

$\sigma^2(Fo^2) = \frac{S^2(C+R^2B)+(pFo^2)^2}{Lp^2}$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarization factor

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{12}H_{11}Br_4NO_2$
Formula Weight	520.84
Crystal Color, Habit	colourless, irregular
Crystal Dimensions	0.20 X 0.16 X 0.08 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (97.8 - 99.9°)
Omega Scan Peak Width	
at Half-height	0.31°
Lattice Parameters	a = 6.322(1)Å b = 13.476(1) Å c = 9.115(2) Å β = 106.54(1)°
	V = 744.5(2) Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	2.323 g/cm^3
F_{000}	492.00
μ(CuKα)	133.48 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R
Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-60.0°C
Scan Type	ω-2θ
Scan Rate	32.0°/min (in ω) (up to 4 scans)
Scan Width	(1.30 + 0.30 tan θ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 1283 Unique: 1170 (R_{int} = 0.062)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.6100 - 1.0000) Secondary Extinction (coefficient: 1.5(3)e-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1134
No. Variables	171
Reflection/Parameter Ratio	6.63
Residuals: R; Rw	0.027 ; 0.033
Goodness of Fit Indicator	2.80
Max Shift/Error in Final Cycle	<0.01
Maximum peak in Final Diff. Map	0.74 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.51 $e^-/Å^3$

Table 1. Atomic Coordinates and Isotropic Displacement Parameters for $C_{12}H_{11}Br_4NO_2$

atom	x	y	z	B_{eq}
Br(4a)	0.0868(2)	-0.0250	-0.1721(1)	2.80(3)
Br(4b)	-0.1009(2)	-0.2429(1)	-0.1830(1)	2.49(2)
Br(5a)	-0.3639(2)	-0.2804	-0.8642(1)	2.37(2)
Br(5b)	0.1380(2)	-0.2185(1)	-0.7381(1)	2.73(3)
O(1)	0.111(1)	-0.4359(5)	-0.3539(8)	2.3(2)
O(3)	0.357(1)	-0.3295(6)	-0.2106(7)	2.2(2)
N(3b')	0.515(2)	-0.0495(8)	-0.361(1)	3.4(2)
C(2)	0.309(2)	-0.4334(8)	-0.226(1)	2.3(2)
C(2')	0.254(2)	-0.4688(9)	-0.085(1)	2.9(3)
C(2")	0.491(2)	-0.4889(9)	-0.265(1)	3.3(3)
C(3a)	0.296(2)	-0.2871(9)	-0.3606(10)	1.8(2)
C(3b)	0.218(2)	-0.1796(8)	-0.355(1)	1.7(2)
C(3b')	0.388(2)	-0.1060(8)	-0.353(1)	2.0(2)
C(4a)	-0.014(2)	-0.1462(8)	-0.448(1)	1.6(2)
C(4b)	-0.165(1)	-0.2210(8)	-0.544(1)	1.7(2)
C(4)	0.041(2)	-0.1498(8)	-0.282(1)	2.0(2)
C(5a)	-0.094(2)	-0.3279(8)	-0.552(1)	1.9(2)
C(5b)	0.135(2)	-0.3640(8)	-0.461(1)	2.1(2)
C(5)	-0.124(1)	-0.2606(8)	-0.6862(10)	1.8(2)
H(2'a)	0.1659	-0.4204	-0.0542	3.4520
H(2'b)	0.1752	-0.5295	-0.1064	3.4520
H(2"a)	0.5160	-0.4612	-0.3544	3.9167
H(2"b)	0.4513	-0.5567	-0.2825	3.9167
H(2"c)	0.6226	-0.4839	-0.1823	3.9167

Table 1. Atomic Coordinates and Isotropic Displacement Parameters for $C_{12}H_{11}Br_4NO_2$ (cont...)

atom	x	y	z	B_{eq}
H(2'c)	0.3865	-0.4787	-0.0049	3.4520
H(3a)	0.4250	-0.2853	-0.3949	2.1586
H(4a)	-0.0224	-0.0816	-0.4912	1.9564
H(4b)	-0.3166	-0.2125	-0.5493	2.0230
H(5a)	-0.2083	-0.3754	-0.5621	2.2500
H(5b)	0.2045	-0.3940	-0.5296	2.4932

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters for $C_{12}H_{11}Br_4NO_2$

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(4a)	0.0395(7)	0.0398(7)	0.0248(5)	-0.0017(6)	0.0053(5)	-0.0115(6)
Br(4b)	0.0295(6)	0.0458(7)	0.0212(5)	-0.0034(5)	0.0101(4)	0.0053(5)
Br(5a)	0.0261(5)	0.0412(7)	0.0170(5)	-0.0018(5)	-0.0036(4)	-0.0014(5)
Br(5b)	0.0258(6)	0.0595(9)	0.0187(5)	-0.0063(6)	0.0069(4)	0.0029(6)
O(1)	0.027(4)	0.028(4)	0.024(4)	-0.005(3)	-0.008(3)	0.001(3)
O(3)	0.036(4)	0.026(4)	0.018(4)	-0.003(3)	0.000(3)	-0.001(3)
N(3b')	0.026(5)	0.052(7)	0.048(6)	-0.013(5)	0.007(4)	0.006(5)
C(2)	0.040(7)	0.027(6)	0.015(5)	-0.004(5)	-0.004(5)	0.003(5)
C(2')	0.040(6)	0.037(7)	0.027(6)	-0.006(6)	0.001(5)	0.003(5)
C(2")	0.036(6)	0.038(7)	0.041(7)	0.008(6)	-0.002(6)	0.003(6)
C(3a)	0.021(5)	0.038(6)	0.006(4)	-0.008(5)	-0.001(4)	-0.005(5)
C(3b)	0.015(5)	0.034(6)	0.013(5)	-0.001(5)	0.000(4)	0.003(4)
C(3b')	0.027(6)	0.033(6)	0.016(5)	0.002(5)	0.002(4)	-0.001(5)
C(4a)	0.019(5)	0.024(6)	0.020(5)	-0.001(4)	0.009(4)	0.000(4)
C(4b)	0.016(5)	0.032(6)	0.016(5)	-0.001(5)	0.005(4)	0.008(5)
C(4)	0.020(5)	0.037(6)	0.018(5)	-0.007(5)	0.004(4)	0.000(5)
C(5a)	0.014(5)	0.032(6)	0.023(6)	-0.003(5)	0.001(4)	0.004(5)
C(5b)	0.026(6)	0.030(6)	0.018(6)	-0.004(5)	-0.002(5)	-0.001(5)
C(5)	0.016(5)	0.039(7)	0.011(4)	-0.001(5)	0.000(4)	-0.008(5)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Interatomic Distances ($\AA$) Involving Non-Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$

atom	atom	distance	atom	atom	distance
Br(4a)	C(4)	1.93(1)	Br(4b)	C(4)	1.910(10)
Br(5a)	C(5)	1.900(9)	Br(5b)	C(5)	1.930(9)
O(1)	C(2)	1.45(1)	O(1)	C(5b)	1.41(1)
O(3)	C(2)	1.43(1)	O(3)	C(3a)	1.43(1)
N(3b')	C(3b')	1.13(1)	C(2)	C(2')	1.50(1)
C(2)	C(2")	1.50(2)	C(3a)	C(3b)	1.54(1)
C(3a)	C(5b)	1.56(1)	C(3b)	C(3b')	1.46(1)
C(3b)	C(4a)	1.54(1)	C(3b)	C(4)	1.51(1)
C(4a)	C(4b)	1.49(1)	C(4a)	C(4)	1.46(1)
C(4b)	C(5a)	1.52(1)	C(4b)	C(5)	1.50(1)
C(5a)	C(5b)	1.53(1)	C(5a)	C(5)	1.49(1)

Table 4. Interatomic Distances ($\AA$) Involving Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$

atom	atom	distance	atom	atom	distance
C(2')	H(2'a)	0.95	C(2')	H(2'b)	0.95
C(2')	H(2'c)	0.95	C(2")	H(2"a)	0.95
C(2")	H(2"b)	0.95	C(2")	H(2"c)	0.95
C(3a)	H(3a)	0.95	C(4a)	H(4a)	0.95
C(4b)	H(4b)	0.95	C(5a)	H(5a)	0.95
C(5b)	H(5b)	0.95			

Table 5. Interatomic Angles(°) Involving Non-Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(1)	C(5b)	107.7(7)	C(2)	O(3)	C(3a)	107.9(8)
O(1)	C(2)	O(3)	102.1(8)	O(1)	C(2)	C(2')	109.0(9)
O(1)	C(2)	C(2")	110.0(9)	O(3)	C(2)	C(2')	108.8(9)
O(3)	C(2)	C(2")	110.8(9)	C(2')	C(2)	C(2")	115.3(10)
O(3)	C(3a)	C(3b)	110.2(8)	O(3)	C(3a)	C(5b)	104.4(8)
C(3b)	C(3a)	C(5b)	119.0(8)	C(3a)	C(3b)	C(3b')	113.4(8)
C(3a)	C(3b)	C(4a)	121.5(8)	C(3a)	C(3b)	C(4)	123.6(8)
C(3b')	C(3b)	C(4a)	113.0(9)	C(3b')	C(3b)	C(4)	116.8(9)
C(4a)	C(3b)	C(4)	57.1(6)	N(3b')	C(3b')	C(3b)	175(1)
C(3b)	C(4a)	C(4b)	118.6(9)	C(3b)	C(4a)	C(4)	60.4(6)
C(4b)	C(4a)	C(4)	120.7(8)	C(4a)	C(4b)	C(5a)	121.4(8)
C(4a)	C(4b)	C(5)	120.5(8)	C(5a)	C(4b)	C(5)	59.3(7)
Br(4a)	C(4)	Br(4b)	110.4(5)	Br(4a)	C(4)	C(3b)	116.0(7)
Br(4a)	C(4)	C(4a)	117.7(8)	Br(4b)	C(4)	C(3b)	122.6(8)
Br(4b)	C(4)	C(4a)	120.5(7)	C(3b)	C(4)	C(4a)	62.4(6)
C(4b)	C(5a)	C(5b)	121.6(9)	C(4b)	C(5a)	C(5)	59.6(6)
C(5b)	C(5a)	C(5)	121.1(8)	O(1)	C(5b)	C(3a)	103.4(8)
O(1)	C(5b)	C(5a)	108.7(8)	C(3a)	C(5b)	C(5a)	118.0(9)
Br(5a)	C(5)	Br(5b)	111.4(4)	Br(5a)	C(5)	C(4b)	119.7(7)
Br(5a)	C(5)	C(5a)	119.9(7)	Br(5b)	C(5)	C(4b)	118.9(7)
Br(5b)	C(5)	C(5a)	117.6(6)	C(4b)	C(5)	C(5a)	61.1(6)

Table 6. Interatomic Angles(°) Involving Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	C(2')	H(2'a)	109.5	C(2)	C(2')	H(2'b)	109.5
C(2)	C(2')	H(2'c)	109.5	H(2'a)	C(2')	H(2'b)	109.5
H(2'a)	C(2')	H(2'c)	109.5	H(2'b)	C(2')	H(2'c)	109.5
C(2)	C(2")	H(2"a)	109.5	C(2)	C(2")	H(2"b)	109.5
C(2)	C(2")	H(2"c)	109.5	H(2"a)	C(2")	H(2"b)	109.5
H(2"a)	C(2")	H(2"c)	109.5	H(2"b)	C(2")	H(2"c)	109.5
O(3)	C(3a)	H(3a)	107.6	C(3b)	C(3a)	H(3a)	107.6
C(5b)	C(3a)	H(3a)	107.6	C(3b)	C(4a)	H(4a)	115.4
C(4b)	C(4a)	H(4a)	115.4	C(4)	C(4a)	H(4a)	115.4
C(4a)	C(4b)	H(4b)	114.8	C(5a)	C(4b)	H(4b)	114.8
C(5)	C(4b)	H(4b)	114.8	C(4b)	C(5a)	H(5a)	114.6
C(5b)	C(5a)	H(5a)	114.6	C(5)	C(5a)	H(5a)	114.6
O(1)	C(5b)	H(5b)	108.8	C(3a)	C(5b)	H(5b)	108.8
C(5a)	C(5b)	H(5b)	108.8				

Table 7. Torsion Angles(°) Involving Non-Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Br(4a)	C(4)	C(3b)	C(3a)	142.3(8)	Br(4a)	C(4)	C(3b)	C(3b')	-7(1).
Br(4a)	C(4)	C(3b)	C(4a)	-109.2(8)	Br(4a)	C(4)	C(4a)	C(3b)	106.5(8)
Br(4a)	C(4)	C(4a)	C(4b)	-145.9(8)	Br(4b)	C(4)	C(3b)	C(3a)	1(1)
Br(4b)	C(4)	C(3b)	C(3b')	-148.5(8)	Br(4b)	C(4)	C(3b)	C(4a)	110.2(9)
Br(4b)	C(4)	C(4a)	C(3b)	-113.5(9)	Br(4b)	C(4)	C(4a)	C(4b)	-5(1)
Br(5a)	C(5)	C(4b)	C(4a)	-139.4(8)	Br(5a)	C(5)	C(4b)	C(5a)	109.9(8)
Br(5a)	C(5)	C(5a)	C(4b)	-109.6(8)	Br(5a)	C(5)	C(5a)	C(5b)	139.6(8)
Br(5b)	C(5)	C(4b)	C(4a)	3(1)	Br(5b)	C(5)	C(4b)	C(5a)	-107.5(8)
Br(5b)	C(5)	C(5a)	C(4b)	109.5(8)	Br(5b)	C(5)	C(5a)	C(5b)	-1(1)
O(1)	C(2)	O(3)	C(3a)	-35.1(10)	O(1)	C(5b)	C(3a)	O(3)	4.4(10)
O(1)	C(5b)	C(3a)	C(3b)	-118.9(9)	O(1)	C(5b)	C(5a)	C(4b)	116.3(10)
O(1)	C(5b)	C(5a)	C(5)	-172.6(9)	O(3)	C(2)	O(1)	C(5b)	38.4(10)
O(3)	C(3a)	C(3b)	C(3b')	98.5(9)	O(3)	C(3a)	C(3b)	C(4a)	-121.6(9)
O(3)	C(3a)	C(3b)	C(4)	-52(1)	O(3)	C(3a)	C(5b)	C(5a)	124.4(9)
N(3b')	C(3b')	C(3b)	C(3a)	86(15)	N(3b')	C(3b')	C(3b)	C(4a)	-56(15)
N(3b')	C(3b')	C(3b)	C(4)	-120(15)	C(2)	O(1)	C(5b)	C(3a)	-26(1)
C(2)	O(1)	C(5b)	C(5a)	-152.4(8)	C(2)	O(3)	C(3a)	C(3b)	148.1(8)
C(2)	O(3)	C(3a)	C(5b)	19(1)	C(2')	C(2)	O(1)	C(5b)	153.5(9)
C(2')	C(2)	O(3)	C(3a)	-150.2(8)	C(2")	C(2)	O(1)	C(5b)	-79(1)
C(2")	C(2)	O(3)	C(3a)	82.1(10)	C(3a)	C(3b)	C(4a)	C(4b)	1(1)
C(3a)	C(3b)	C(4a)	C(4)	112.1(10)	C(3a)	C(3b)	C(4)	C(4a)	-108(1)
C(3a)	C(5b)	C(5a)	C(4b)	0(1)	C(3a)	C(5b)	C(5a)	C(5)	70(1)
C(3b)	C(3a)	C(5b)	C(5a)	1(1)	C(3b)	C(4a)	C(4b)	C(5a)	0(1)
C(3b)	C(4a)	C(4b)	C(5)	-71(1)	C(3b)	C(4)	C(4a)	C(4b)	107(1)

Table 7. Torsion Angles(°) Involving Non-Hydrogen Atoms for $C_{12}H_{11}Br_4NO_2$ (cont...)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(3b')	C(3b)	C(3a)	C(5b)	-141.1(9)	C(3b')	C(3b)	C(4a)	C(4b)	141.1(9)
C(3b')	C(3b)	C(4a)	C(4)	-107.9(10)	C(3b')	C(3b)	C(4)	C(4a)	101.3(10)
C(4a)	C(3b)	C(3a)	C(5b)	-1(1)	C(4a)	C(4b)	C(5a)	C(5b)	0(1)
C(4a)	C(4b)	C(5a)	C(5)	-109.2(10)	C(4a)	C(4b)	C(5)	C(5a)	110(1)
C(4b)	C(4a)	C(3b)	C(4)	-111.0(10)	C(4b)	C(5)	C(5a)	C(5b)	-110(1)
C(4)	C(3b)	C(3a)	C(5b)	67(1)	C(4)	C(4a)	C(4b)	C(5a)	-71(1)
C(4)	C(4a)	C(4b)	C(5)	-142.0(10)	C(5b)	C(5a)	C(4b)	C(5)	109(1)

Table 8. Non-bonded Contacts out to 3.60 $\AA$ for $C_{12}H_{11}Br_4NO_2$

atom	atom	distance	ADC	atom	atom	distance	ADC
Br(4a)	N(3b')	3.547(9)	45501	Br(4b)	O(3)	3.560(7)	45501
Br(5a)	O(3)	3.217(7)	45401	O(1)	C(4a)	3.32(1)	54402
N(3b')	C(4)	3.47(1)	65501	N(3b')	C(2")	3.50(2)	65402
N(3b')	C(4a)	3.54(1)	65501				

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

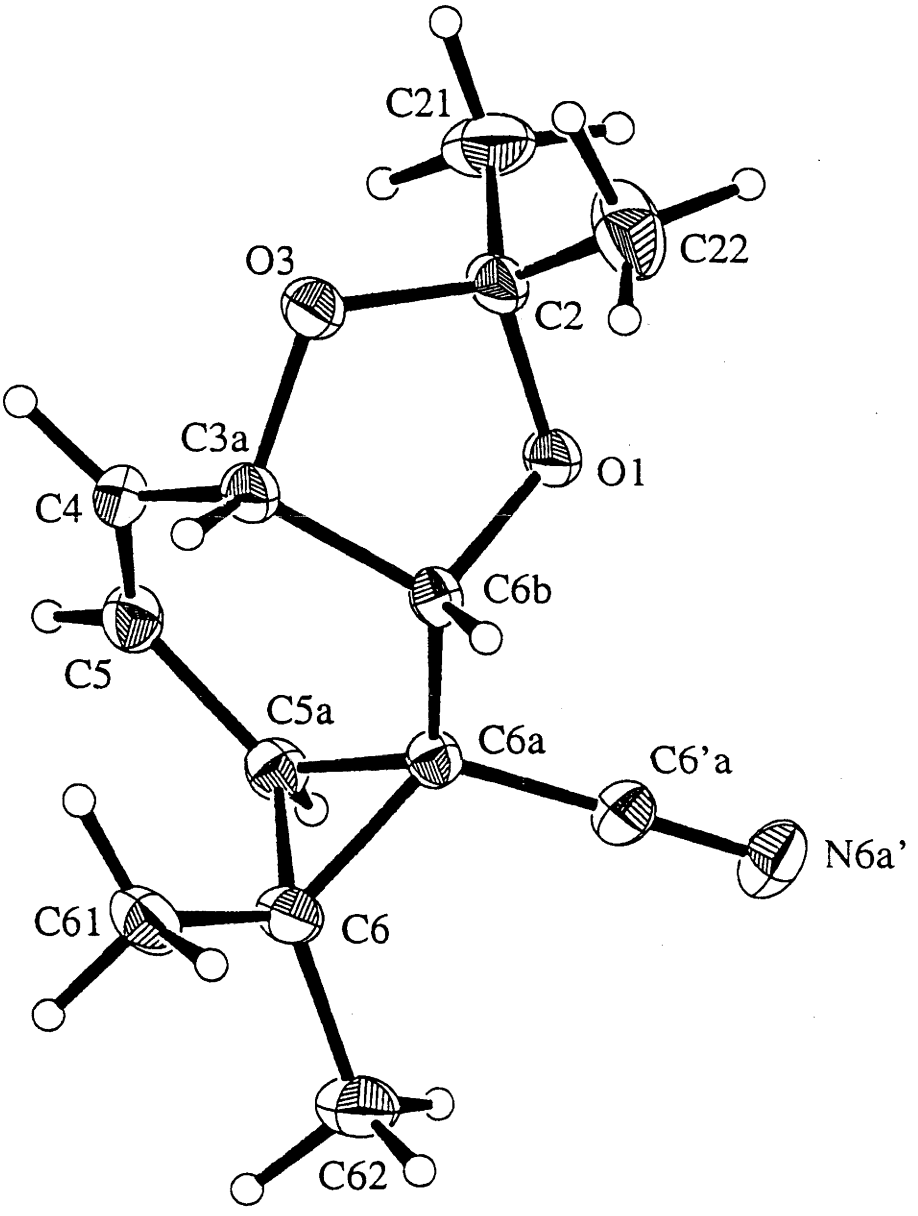
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	1/2+Y,	-Z

1.2 X-Ray Structure Report for Compound 66*



* X-ray crystal data are presented as provided by Dr. David Hockless (Research School of Chemistry, ANU).

Experimental

Data Collection

A colorless irregular crystal of $C_{13}H_{17}NO_2$ having approximate dimensions of 0.34 x 0.14 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $73.75 < 2\theta < 88.94°$ corresponded to a primitive monoclinic cell with dimensions:

$$\begin{aligned} a &= 8.942(1)\ \AA \\ b &= 8.0016(9)\ \AA \qquad \beta = 110.312(8)° \\ c &= 9.169(1)\ \AA \\ V &= 615.2(1)\ \AA^3 \end{aligned}$$

For Z = 2 and F.W. = 219.28, the calculated density is 1.18 g/cm^3. Based on the systematic absences of:

$$0k0:\ k \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P2_1\ (\#4)$$

The data were collected at a temperature of 23 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.30° with a take-off angle of 6.0°. Scans of $(1.30 + 0.30 \tan \theta)°$ were made at a speed of 8.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 1061 reflections which were collected, 995 were unique ($R_{int} = 0.029$). The intensities of three representative reflection were measured after every 150 reflections. Over the course of data collection, the standards decreased by 15.9%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Cu-Kα radiation is 6.0 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in

transmission factors ranging from 0.98 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 1.26712e-05).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[3] was based on 918 observed reflections (I > 3.00σ(I)) and 213 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.026$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.031$$

The standard deviation of an observation of unit weight[4] was 1.90. The weighting scheme was based on counting statistics and included a factor (p = 0.019) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.07 and -0.09 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{13}H_{17}NO_2$
Formula Weight	219.28
Crystal Color, Habit	colorless, irregular
Crystal Dimensions	0.34 X 0.14 X 0.10 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (73.8 - 88.9°)
Omega Scan Peak Width	
at Half-height	0.30°
Lattice Parameters	a = 8.942(1)Å b = 8.0016(9) Å c = 9.169(1) Å β = 110.312(8)°
	V = 615.2(1) Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.184 g/cm^3
F_{000}	236.00
μ(CuKα)	6.04 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R

Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	23.0°C
Scan Type	ω-2θ
Scan Rate	8.0°/min (in ω) (up to 4 scans)
Scan Width	(1.30 + 0.30 tan θ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 1061 Unique: 995 (R_{int} = 0.029)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9792 - 1.0000) Decay (15.86% decline) Secondary Extinction (coefficient: 1.26712e-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0190
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	918
No. Variables	213
Reflection/Parameter Ratio	4.31
Residuals: R; Rw	0.026 ; 0.031

Goodness of Fit Indicator	1.90
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.07 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.09 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.8491(2)	0.2328	0.6896(2)	3.93(4)
O(3)	0.8683(2)	0.5116(3)	0.7484(2)	5.00(4)
N(6a')	0.6718(3)	-0.0960(4)	0.4472(3)	5.56(7)
C(2)	0.9191(3)	0.3492(4)	0.8114(3)	4.42(6)
C(3a)	0.7766(3)	0.4950(4)	0.5860(3)	3.88(5)
C(4)	0.8741(3)	0.5316(5)	0.4868(3)	4.30(6)
C(5)	0.8723(3)	0.4411(4)	0.3670(3)	4.36(7)
C(5a)	0.7715(3)	0.2912(4)	0.3141(3)	3.93(6)
C(6)	0.5914(3)	0.2988(4)	0.2639(3)	4.13(6)
C(6a)	0.6894(3)	0.2249(4)	0.4223(3)	3.44(5)
C(6b)	0.7174(3)	0.3152(4)	0.5747(3)	3.36(5)
C(6'a)	0.6813(3)	0.0447(5)	0.4372(3)	3.93(6)
C(21)	1.0991(4)	0.3344(6)	0.8557(6)	7.5(1)
C(22)	0.8593(8)	0.3223(7)	0.9438(5)	7.9(1)
C(61)	0.5053(4)	0.4628(5)	0.2537(4)	5.13(7)
C(62)	0.4986(4)	0.1754(6)	0.1408(4)	5.78(9)
H(3a)	0.690(3)	0.571(4)	0.567(3)	3.9(6)
H(4)	0.940(3)	0.632(4)	0.514(3)	5.2(7)
H(5)	0.939(3)	0.466(4)	0.305(3)	4.7(6)
H(5a)	0.819(3)	0.206(4)	0.261(3)	4.4(6)
H(6b)	0.622(2)	0.309(3)	0.600(2)	2.5(4)
H(21a)	1.135(7)	0.371(9)	0.761(7)	17(2)
H(21b)	1.150(5)	0.419(6)	0.939(5)	10(1)
H(21c)	1.131(5)	0.225(7)	0.902(5)	10(1)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(22a)	0.744(5)	0.338(6)	0.910(4)	9(1)
H(22b)	0.918(4)	0.222(5)	1.002(5)	8.2(9)
H(22c)	0.897(5)	0.420(6)	1.018(5)	10(1)
H(61a)	0.464(4)	0.502(6)	0.144(5)	9(1)
H(61b)	0.404(5)	0.446(6)	0.283(4)	10(1)
H(61c)	0.568(4)	0.555(5)	0.320(4)	6.1(8)
H(62a)	0.471(4)	0.225(5)	0.033(4)	8.0(9)
H(62b)	0.388(4)	0.153(5)	0.155(4)	6.9(8)
H(62c)	0.554(4)	0.077(5)	0.142(4)	6.1(8)

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.059(1)	0.034(1)	0.0454(9)	0.0060(8)	0.0042(8)	0.0023(8)
O(3)	0.090(1)	0.039(1)	0.046(1)	0.004(1)	0.0042(9)	-0.0013(9)
N(6a')	0.072(2)	0.042(2)	0.098(2)	-0.008(1)	0.031(1)	-0.004(1)
C(2)	0.073(2)	0.039(2)	0.044(1)	0.010(1)	0.006(1)	0.001(1)
C(3a)	0.057(1)	0.037(1)	0.046(1)	0.006(1)	0.009(1)	0.003(1)
C(4)	0.057(1)	0.042(2)	0.057(2)	-0.010(1)	0.009(1)	0.010(1)
C(5)	0.054(1)	0.059(2)	0.055(2)	-0.006(1)	0.021(1)	0.011(1)
C(5a)	0.051(1)	0.050(2)	0.048(1)	0.002(1)	0.018(1)	0.000(1)
C(6)	0.051(1)	0.058(2)	0.043(1)	0.001(1)	0.009(1)	0.000(1)
C(6a)	0.043(1)	0.039(1)	0.047(1)	0.002(1)	0.013(1)	0.002(1)
C(6b)	0.044(1)	0.038(1)	0.044(1)	0.006(1)	0.013(1)	0.006(1)
C(6'a)	0.046(1)	0.048(2)	0.057(2)	-0.004(1)	0.020(1)	-0.002(1)
C(21)	0.074(2)	0.067(3)	0.104(3)	0.009(2)	-0.021(2)	-0.017(3)
C(22)	0.178(5)	0.070(3)	0.065(2)	0.021(3)	0.057(3)	0.010(2)
C(61)	0.067(2)	0.067(2)	0.052(2)	0.016(2)	0.008(1)	0.013(2)
C(62)	0.071(2)	0.081(3)	0.055(2)	-0.003(2)	0.006(2)	-0.013(2)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(1)	C(2)	1.422(3)	O(1)	C(6b)	1.439(3)
O(3)	C(2)	1.431(3)	O(3)	C(3a)	1.435(3)
N(6a')	C(6'a)	1.135(4)	C(2)	C(21)	1.522(5)
C(2)	C(22)	1.503(5)	C(3a)	C(4)	1.490(4)
C(3a)	C(6b)	1.525(4)	C(4)	C(5)	1.311(4)
C(5)	C(5a)	1.477(4)	C(5a)	C(6)	1.515(4)
C(5a)	C(6a)	1.520(3)	C(6)	C(6a)	1.531(3)
C(6)	C(61)	1.508(4)	C(6)	C(62)	1.512(4)
C(6a)	C(6b)	1.515(3)	C(6a)	C(6'a)	1.452(5)

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C(3a)	H(3a)	0.95(3)	C(4)	H(4)	0.97(3)
C(5)	H(5)	0.97(3)	C(5a)	H(5a)	1.02(3)
C(6b)	H(6b)	0.96(2)	C(21)	H(21a)	1.07(6)
C(21)	H(21b)	1.00(5)	C(21)	H(21c)	0.97(6)
C(22)	H(22a)	0.98(4)	C(22)	H(22b)	1.01(4)
C(22)	H(22c)	1.01(5)	C(61)	H(61a)	0.99(4)
C(61)	H(61b)	1.04(4)	C(61)	H(61c)	1.00(4)
C(62)	H(62a)	1.02(3)	C(62)	H(62b)	1.05(3)
C(62)	H(62c)	0.93(4)			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(1)	C(6b)	107.5(2)	C(2)	O(3)	C(3a)	108.8(2)
O(1)	C(2)	O(3)	106.6(2)	O(1)	C(2)	C(21)	107.2(3)
O(1)	C(2)	C(22)	110.9(3)	O(3)	C(2)	C(21)	109.7(3)
O(3)	C(2)	C(22)	107.7(3)	C(21)	C(2)	C(22)	114.4(3)
O(3)	C(3a)	C(4)	111.8(2)	O(3)	C(3a)	C(6b)	102.6(2)
C(4)	C(3a)	C(6b)	114.0(2)	C(3a)	C(4)	C(5)	124.2(3)
C(4)	C(5)	C(5a)	123.5(2)	C(5)	C(5a)	C(6)	122.0(2)
C(5)	C(5a)	C(6a)	116.5(2)	C(6)	C(5a)	C(6a)	60.6(2)
C(5a)	C(6)	C(6a)	59.9(2)	C(5a)	C(6)	C(61)	121.3(3)
C(5a)	C(6)	C(62)	116.8(3)	C(6a)	C(6)	C(61)	120.4(2)
C(6a)	C(6)	C(62)	116.1(3)	C(61)	C(6)	C(62)	112.7(3)
C(5a)	C(6a)	C(6)	59.5(2)	C(5a)	C(6a)	C(6b)	118.2(2)
C(5a)	C(6a)	C(6'a)	117.4(2)	C(6)	C(6a)	C(6b)	123.2(2)
C(6)	C(6a)	C(6'a)	116.2(2)	C(6b)	C(6a)	C(6'a)	112.6(2)
O(1)	C(6b)	C(3a)	101.9(2)	O(1)	C(6b)	C(6a)	106.7(2)
C(3a)	C(6b)	C(6a)	117.0(2)	N(6a')	C(6'a)	C(6a)	178.7(3)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O(3)	C(3a)	H(3a)	105(2)	C(4)	C(3a)	H(3a)	112(2)
C(6b)	C(3a)	H(3a)	111(2)	C(3a)	C(4)	H(4)	116(2)
C(5)	C(4)	H(4)	120(2)	C(4)	C(5)	H(5)	123(2)
C(5a)	C(5)	H(5)	114(2)	C(5)	C(5a)	H(5a)	113(2)
C(6)	C(5a)	H(5a)	117(2)	C(6a)	C(5a)	H(5a)	117(2)
O(1)	C(6b)	H(6b)	112(1)	C(3a)	C(6b)	H(6b)	110(1)
C(6a)	C(6b)	H(6b)	109(1)	C(2)	C(21)	H(21a)	111(3)
C(2)	C(21)	H(21b)	108(2)	C(2)	C(21)	H(21c)	108(3)
H(21a)	C(21)	H(21b)	105(4)	H(21a)	C(21)	H(21c)	118(5)
H(21b)	C(21)	H(21c)	107(3)	C(2)	C(22)	H(22a)	111(2)
C(2)	C(22)	H(22b)	106(2)	C(2)	C(22)	H(22c)	107(3)
H(22a)	C(22)	H(22b)	124(4)	H(22a)	C(22)	H(22c)	101(4)
H(22b)	C(22)	H(22c)	106(3)	C(6)	C(61)	H(61a)	110(3)
C(6)	C(61)	H(61b)	110(3)	C(6)	C(61)	H(61c)	116(2)
H(61a)	C(61)	H(61b)	105(3)	H(61a)	C(61)	H(61c)	108(3)
H(61b)	C(61)	H(61c)	107(3)	C(6)	C(62)	H(62a)	111(2)
C(6)	C(62)	H(62b)	108(2)	C(6)	C(62)	H(62c)	113(2)
H(62a)	C(62)	H(62b)	105(3)	H(62a)	C(62)	H(62c)	107(3)
H(62b)	C(62)	H(62c)	112(3)				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(1)	C(2)	O(3)	C(3a)	-3.9(3)	O(1)	C(6b)	C(3a)	O(3)	-34.3(2)
O(1)	C(6b)	C(3a)	C(4)	86.7(2)	O(1)	C(6b)	C(6a)	C(5a)	-92.9(2)
O(1)	C(6b)	C(6a)	C(6)	-163.3(2)	O(1)	C(6b)	C(6a)	C(6'a)	49.1(3)
O(3)	C(2)	O(1)	C(6b)	-19.4(3)	O(3)	C(3a)	C(4)	C(5)	135.6(3)
O(3)	C(3a)	C(6b)	C(6a)	-150.2(2)	N(6a')	C(6'a)	C(6a)	C(5a)	-105.5(1)
N(6a')	C(6'a)	C(6a)	C(6)	-37.9(1)	N(6a')	C(6'a)	C(6a)	C(6b)	112.1(1)
C(2)	O(1)	C(6b)	C(3a)	33.2(2)	C(2)	O(1)	C(6b)	C(6a)	156.4(2)
C(2)	O(3)	C(3a)	C(4)	-98.8(3)	C(2)	O(3)	C(3a)	C(6b)	23.8(3)
C(3a)	O(3)	C(2)	C(21)	111.8(3)	C(3a)	O(3)	C(2)	C(22)	-123.0(3)
C(3a)	C(4)	C(5)	C(5a)	0.6(4)	C(3a)	C(6b)	C(6a)	C(5a)	20.3(3)
C(3a)	C(6b)	C(6a)	C(6)	-50.1(3)	C(3a)	C(6b)	C(6a)	C(6'a)	162.3(2)
C(4)	C(3a)	C(6b)	C(6a)	-29.2(3)	C(4)	C(5)	C(5a)	C(6)	59.5(4)
C(4)	C(5)	C(5a)	C(6a)	-10.9(4)	C(5)	C(4)	C(3a)	C(6b)	19.8(3)
C(5)	C(5a)	C(6)	C(6a)	-104.6(3)	C(5)	C(5a)	C(6)	C(61)	4.8(4)
C(5)	C(5a)	C(6)	C(62)	149.3(3)	C(5)	C(5a)	C(6a)	C(6)	113.5(3)
C(5)	C(5a)	C(6a)	C(6b)	-0.4(3)	C(5)	C(5a)	C(6a)	C(6'a)	-140.6(2)
C(5a)	C(6)	C(6a)	C(6b)	105.7(3)	C(5a)	C(6)	C(6a)	C(6'a)	-107.7(3)
C(5a)	C(6a)	C(6)	C(61)	-110.8(3)	C(5a)	C(6a)	C(6)	C(62)	107.2(3)
C(6)	C(5a)	C(6a)	C(6b)	-113.9(3)	C(6)	C(5a)	C(6a)	C(6'a)	105.8(3)
C(6a)	C(5a)	C(6)	C(61)	109.4(3)	C(6a)	C(5a)	C(6)	C(62)	-106.1(3)
C(6b)	O(1)	C(2)	C(21)	-136.8(3)	C(6b)	O(1)	C(2)	C(22)	97.6(3)
C(6b)	C(6a)	C(6)	C(61)	-5.1(4)	C(6b)	C(6a)	C(6)	C(62)	-147.1(3)
C(6'a)	C(6a)	C(6)	C(61)	141.4(3)	C(6'a)	C(6a)	C(6)	C(62)	-0.6(3)

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(5)	3.581(3)	74602	N(6a')	C(4)	3.439(4)	54501
N(6a')	C(6b)	3.488(4)	64602	N(6a')	C(3a)	3.518(4)	54501

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

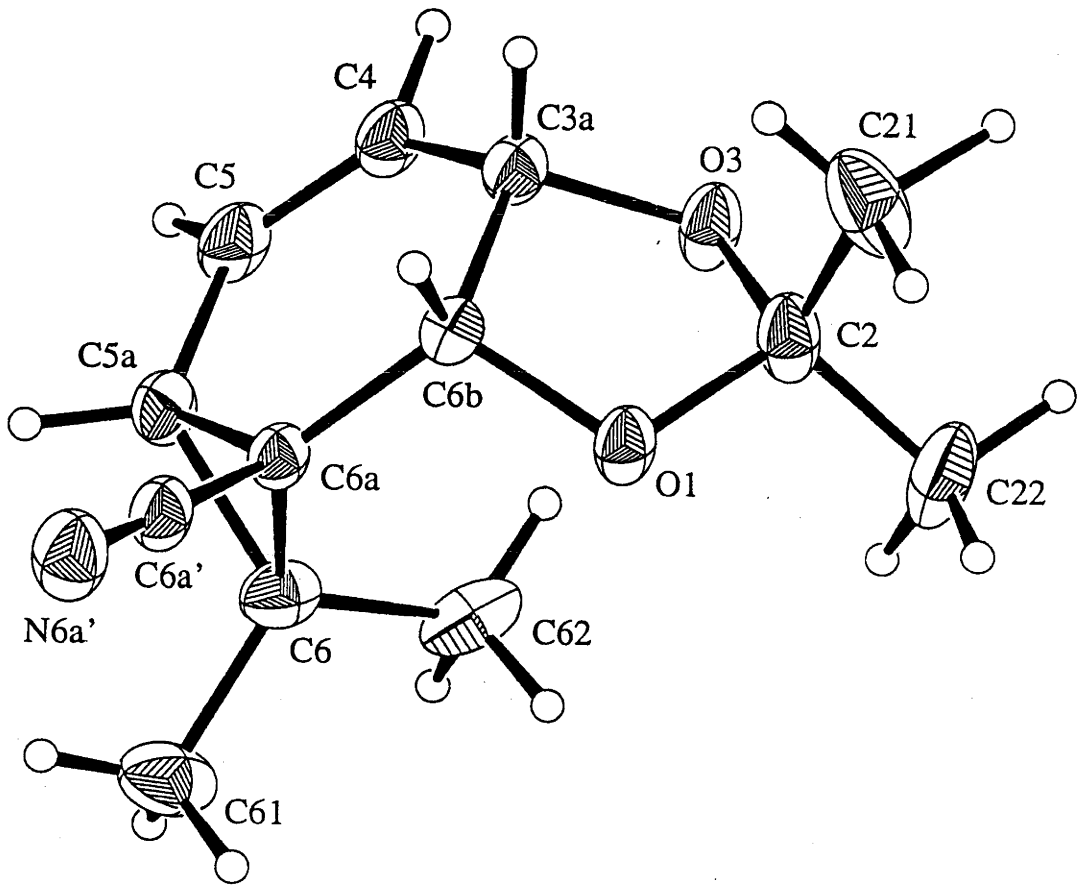
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) X, Y, Z (2) -X, 1/2+Y, -Z

1.3 X-Ray Structure Report for Compound 65*



* X-ray crystal data are presented as provided by Dr. David Hockless (Research School of Chemistry, ANU).

Experimental

Data Collection

A colorless plate crystal of $C_{13}H_{17}O_2N$ having approximate dimensions of 0.34 x 0.28 x 0.08 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 22 carefully centered reflections in the range $50.07 < 2\theta < 81.97°$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 11.745(1)\ \AA$$
$$b = 11.918(1)\ \AA$$
$$c = 8.879(2)\ \AA$$
$$V = 1242.9(3)\ \AA^3$$

For Z = 4 and F.W. = 219.28, the calculated density is 1.17 g/cm^3. The systematic absences of:

$$h00:\ h \neq 2n$$
$$0k0:\ k \neq 2n$$
$$00l:\ l \neq 2n$$

uniquely determine the space group to be:

$$P2_12_12_1\ (\#19)$$

The data were collected at a temperature of -60 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take-off angle of 6.0°. Scans of $(1.10 + 0.30 \tan \theta)°$ were made at a speed of 8.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

A total of 1104 reflections was collected. The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 6.0 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted

in transmission factors ranging from 0.90 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 9.3(7)e-06).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[3] was based on 934 observed reflections (I > 3.00σ(I)) and 214 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.030$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.032$$

The standard deviation of an observation of unit weight[4] was 2.17. The weighting scheme was based on counting statistics and included a factor (p = 0.012) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.12 and -0.08 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{13}H_{17}O_2N$
Formula Weight	219.28
Crystal Color, Habit	colorless, plate
Crystal Dimensions	0.34 X 0.28 X 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	22 (50.1 - 82.0°)
Omega Scan Peak Width	
at Half-height	0.32°
Lattice Parameters	a = 11.745(1)Å b = 11.918(1) Å c = 8.879(2) Å
	V = 1242.9(3) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.172 g/cm^3
F_{000}	472.00
μ(CuKα)	5.98 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R
Radiation	CuKα (λ = 1.54178 Å)

	graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-60.0°C
Scan Type	ω-2θ
Scan Rate	8.0°/min (in ω) (up to 4 scans)
Scan Width	$(1.10 + 0.30 \tan \theta)°$
$2\theta_{max}$	120.0°
No. of Reflections Measured	Total: 1104
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9044 - 1.0000) Secondary Extinction (coefficient: 9.3(7)e-06)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4} Fo^2]^{-1}$
p-factor	0.0120
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	934
No. Variables	214
Reflection/Parameter Ratio	4.36
Residuals: R; Rw	0.030 ; 0.032
Goodness of Fit Indicator	2.17

Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.12 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.08 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.0955(2)	0.1383(1)	0.9254(2)	4.67(5)
O(3)	0.2014(2)	0.0476(2)	1.0983(2)	5.37(5)
N(6a')	-0.0284(3)	0.0131(2)	0.5270(3)	6.93(9)
C(2)	0.1732(3)	0.1577(2)	1.0461(4)	5.88(9)
C(3a)	0.2083(3)	-0.0220(2)	0.9660(3)	4.60(7)
C(4)	0.1827(3)	-0.1407(2)	1.0073(4)	5.16(8)
C(5)	0.0957(3)	-0.1967(2)	0.9565(4)	5.30(8)
C(5a)	0.0074(3)	-0.1507(2)	0.8561(4)	4.87(7)
C(6)	-0.0749(2)	-0.0620(2)	0.9098(4)	5.14(8)
C(6a)	0.0225(2)	-0.0291(2)	0.8051(3)	3.94(6)
C(6b)	0.1274(2)	0.0349(2)	0.8543(3)	3.87(6)
C(6a')	-0.0075(3)	-0.0060(2)	0.6501(4)	4.79(7)
C(21)	0.2792(5)	0.2179(4)	0.9923(7)	8.5(1)
C(22)	0.1119(5)	0.2183(4)	1.1711(5)	8.5(1)
C(61)	-0.1940(3)	-0.0621(4)	0.8419(8)	7.6(1)
C(62)	-0.0718(4)	-0.0247(4)	1.0744(5)	6.6(1)
H(3a)	0.282(2)	-0.017(2)	0.922(3)	4.9(7)
H(4)	0.242(3)	-0.175(3)	1.074(4)	6.9(9)
H(5)	0.082(3)	-0.272(3)	0.998(4)	8.1(9)
H(5a)	-0.023(2)	-0.200(3)	0.782(3)	5.4(7)
H(6b)	0.170(2)	0.049(2)	0.766(3)	3.4(6)
H(21a)	0.316(3)	0.180(3)	0.909(4)	7(1)
H(21b)	0.255(3)	0.291(4)	0.948(5)	11(1)
H(21c)	0.334(4)	0.230(4)	1.096(6)	15(1)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(22a)	0.169(3)	0.234(3)	1.255(5)	10(1)
H(22b)	0.083(3)	0.281(3)	1.137(4)	9(1)
H(22c)	0.041(4)	0.171(4)	1.211(5)	13(2)
H(61a)	-0.193(4)	-0.091(4)	0.736(5)	11(1)
H(61b)	-0.237(3)	-0.103(4)	0.904(5)	10(1)
H(61c)	-0.220(3)	0.016(3)	0.820(4)	7.4(9)
H(62a)	-0.131(3)	-0.068(3)	1.125(4)	8(1)
H(62b)	-0.101(2)	0.048(3)	1.074(4)	5.8(7)
H(62c)	0.000(3)	-0.027(3)	1.126(4)	5.7(9)

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.082(1)	0.0353(9)	0.060(1)	0.004(1)	-0.016(1)	-0.003(1)
O(3)	0.105(2)	0.041(1)	0.058(1)	0.014(1)	-0.024(1)	-0.005(1)
N(6a')	0.114(2)	0.076(2)	0.073(2)	0.015(2)	-0.029(2)	-0.009(2)
C(2)	0.109(3)	0.043(2)	0.072(2)	0.007(2)	-0.038(2)	-0.005(2)
C(3a)	0.065(2)	0.048(2)	0.062(2)	0.007(2)	-0.007(2)	-0.008(2)
C(4)	0.086(3)	0.043(2)	0.067(2)	0.017(2)	-0.014(2)	-0.005(2)
C(5)	0.088(2)	0.035(1)	0.079(2)	0.010(2)	-0.005(2)	0.001(2)
C(5a)	0.070(2)	0.036(1)	0.078(2)	-0.001(2)	-0.008(2)	-0.005(2)
C(6)	0.059(2)	0.044(2)	0.092(2)	0.001(1)	0.012(2)	0.006(2)
C(6a)	0.058(2)	0.037(1)	0.055(2)	0.004(1)	-0.004(1)	-0.003(1)
C(6b)	0.057(2)	0.044(1)	0.046(2)	0.000(1)	0.003(1)	-0.001(1)
C(6a')	0.074(2)	0.044(2)	0.064(2)	0.006(2)	-0.012(2)	-0.007(2)
C(21)	0.119(4)	0.070(3)	0.132(4)	-0.029(3)	-0.054(4)	0.014(3)
C(22)	0.175(5)	0.063(2)	0.083(3)	0.044(3)	-0.044(4)	-0.029(2)
C(61)	0.059(2)	0.069(3)	0.161(5)	-0.009(2)	-0.003(3)	0.011(3)
C(62)	0.092(3)	0.059(2)	0.099(3)	0.022(2)	0.044(3)	0.018(2)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(1)	C(2)	1.426(3)	O(1)	C(6b)	1.434(3)
O(3)	C(2)	1.430(3)	O(3)	C(3a)	1.441(3)
N(6a')	C(6a')	1.143(4)	C(2)	C(21)	1.515(6)
C(2)	C(22)	1.508(5)	C(3a)	C(4)	1.492(4)
C(3a)	C(6b)	1.531(4)	C(4)	C(5)	1.302(4)
C(5)	C(5a)	1.474(4)	C(5a)	C(6)	1.510(4)
C(5a)	C(6a)	1.528(4)	C(6)	C(6a)	1.525(4)
C(6)	C(61)	1.524(5)	C(6)	C(62)	1.528(6)
C(6a)	C(6b)	1.514(4)	C(6a)	C(6a')	1.447(4)

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C(3a)	H(3a)	0.95(3)	C(4)	H(4)	1.00(3)
C(5)	H(5)	0.99(3)	C(5a)	H(5a)	0.95(3)
C(6b)	H(6b)	0.94(2)	C(21)	H(21a)	0.97(3)
C(21)	H(21b)	1.00(5)	C(21)	H(21c)	1.13(6)
C(22)	H(22a)	1.02(4)	C(22)	H(22b)	0.87(4)
C(22)	H(22c)	1.06(4)	C(61)	H(61a)	1.00(4)
C(61)	H(61b)	0.89(4)	C(61)	H(61c)	1.00(4)
C(62)	H(62a)	0.97(4)	C(62)	H(62b)	0.93(3)
C(62)	H(62c)	0.95(3)			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(1)	C(6b)	107.6(2)	C(2)	O(3)	C(3a)	106.1(2)
O(1)	C(2)	O(3)	104.1(2)	O(1)	C(2)	C(21)	111.5(3)
O(1)	C(2)	C(22)	109.0(3)	O(3)	C(2)	C(21)	110.3(3)
O(3)	C(2)	C(22)	108.1(3)	C(21)	C(2)	C(22)	113.4(4)
O(3)	C(3a)	C(4)	109.5(3)	O(3)	C(3a)	C(6b)	103.8(2)
C(4)	C(3a)	C(6b)	117.0(3)	C(3a)	C(4)	C(5)	124.0(3)
C(4)	C(5)	C(5a)	124.8(3)	C(5)	C(5a)	C(6)	121.3(3)
C(5)	C(5a)	C(6a)	116.8(3)	C(6)	C(5a)	C(6a)	60.3(2)
C(5a)	C(6)	C(6a)	60.5(2)	C(5a)	C(6)	C(61)	117.6(3)
C(5a)	C(6)	C(62)	119.4(3)	C(6a)	C(6)	C(61)	116.6(3)
C(6a)	C(6)	C(62)	119.4(3)	C(61)	C(6)	C(62)	113.6(4)
C(5a)	C(6a)	C(6)	59.3(2)	C(5a)	C(6a)	C(6b)	119.1(2)
C(5a)	C(6a)	C(6a')	115.7(3)	C(6)	C(6a)	C(6b)	124.3(3)
C(6)	C(6a)	C(6a')	116.5(3)	C(6b)	C(6a)	C(6a')	112.1(2)
O(1)	C(6b)	C(3a)	105.0(2)	O(1)	C(6b)	C(6a)	110.3(2)
C(3a)	C(6b)	C(6a)	117.9(2)	N(6a')	C(6a')	C(6a)	178.3(4)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
O(3)	C(3a)	H(3a)	110(2)	C(4)	C(3a)	H(3a)	110(2)
C(6b)	C(3a)	H(3a)	106(2)	C(3a)	C(4)	H(4)	113(2)
C(5)	C(4)	H(4)	123(2)	C(4)	C(5)	H(5)	118(2)
C(5a)	C(5)	H(5)	117(2)	C(5)	C(5a)	H(5a)	117(2)
C(6)	C(5a)	H(5a)	114(2)	C(6a)	C(5a)	H(5a)	115(2)
O(1)	C(6b)	H(6b)	111(2)	C(3a)	C(6b)	H(6b)	106(1)
C(6a)	C(6b)	H(6b)	107(1)	C(2)	C(21)	H(21a)	113(2)
C(2)	C(21)	H(21b)	108(3)	C(2)	C(21)	H(21c)	106(3)
H(21a)	C(21)	H(21b)	103(4)	H(21a)	C(21)	H(21c)	115(3)
H(21b)	C(21)	H(21c)	112(3)	C(2)	C(22)	H(22a)	108(2)
C(2)	C(22)	H(22b)	110(3)	C(2)	C(22)	H(22c)	111(3)
H(22a)	C(22)	H(22b)	110(3)	H(22a)	C(22)	H(22c)	111(3)
H(22b)	C(22)	H(22c)	106(4)	C(6)	C(61)	H(61a)	111(3)
C(6)	C(61)	H(61b)	106(3)	C(6)	C(61)	H(61c)	111(2)
H(61a)	C(61)	H(61b)	114(4)	H(61a)	C(61)	H(61c)	98(3)
H(61b)	C(61)	H(61c)	117(4)	C(6)	C(62)	H(62a)	106(2)
C(6)	C(62)	H(62b)	105(2)	C(6)	C(62)	H(62c)	118(2)
H(62a)	C(62)	H(62b)	103(3)	H(62a)	C(62)	H(62c)	113(3)
H(62b)	C(62)	H(62c)	111(3)				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(1)	C(2)	O(3)	C(3a)	37.7(3)	O(1)	C(6b)	C(3a)	O(3)	7.8(3)
O(1)	C(6b)	C(3a)	C(4)	128.6(3)	O(1)	C(6b)	C(6a)	C(5a)	-126.3(3)
O(1)	C(6b)	C(6a)	C(6)	-55.4(3)	O(1)	C(6b)	C(6a)	C(6a')	94.0(3)
O(3)	C(2)	O(1)	C(6b)	-32.5(3)	O(3)	C(3a)	C(4)	C(5)	116.4(4)
O(3)	C(3a)	C(6b)	C(6a)	-115.5(3)	N(6a')	C(6a')	C(6a)	C(5a)	-120.1(1)
N(6a')	C(6a')	C(6a)	C(6)	173.1(1)	N(6a')	C(6a')	C(6a)	C(6b)	21.1(1)
C(2)	O(1)	C(6b)	C(3a)	15.0(3)	C(2)	O(1)	C(6b)	C(6a)	143.0(2)
C(2)	O(3)	C(3a)	C(4)	-153.5(3)	C(2)	O(3)	C(3a)	C(6b)	-27.8(3)
C(3a)	O(3)	C(2)	C(21)	-82.0(4)	C(3a)	O(3)	C(2)	C(22)	153.5(3)
C(3a)	C(4)	C(5)	C(5a)	-2.5(6)	C(3a)	C(6b)	C(6a)	C(5a)	-5.8(4)
C(3a)	C(6b)	C(6a)	C(6)	65.1(4)	C(3a)	C(6b)	C(6a)	C(6a')	-145.5(3)
C(4)	C(3a)	C(6b)	C(6a)	5.3(4)	C(4)	C(5)	C(5a)	C(6)	-68.0(5)
C(4)	C(5)	C(5a)	C(6a)	2.0(5)	C(5)	C(4)	C(3a)	C(6b)	-1.3(5)
C(5)	C(5a)	C(6)	C(6a)	105.1(3)	C(5)	C(5a)	C(6)	C(61)	-148.4(4)
C(5)	C(5a)	C(6)	C(62)	-4.1(4)	C(5)	C(5a)	C(6a)	C(6)	-112.5(3)
C(5)	C(5a)	C(6a)	C(6b)	2.3(4)	C(5)	C(5a)	C(6a)	C(6a')	140.7(3)
C(5a)	C(6)	C(6a)	C(6b)	-106.3(3)	C(5a)	C(6)	C(6a)	C(6a')	105.5(3)
C(5a)	C(6a)	C(6)	C(61)	-108.1(3)	C(5a)	C(6a)	C(6)	C(62)	109.2(3)
C(6)	C(5a)	C(6a)	C(6b)	114.8(3)	C(6)	C(5a)	C(6a)	C(6a')	-106.8(3)
C(6a)	C(5a)	C(6)	C(61)	106.6(4)	C(6a)	C(5a)	C(6)	C(62)	-109.1(3)
C(6b)	O(1)	C(2)	C(21)	86.3(3)	C(6b)	O(1)	C(2)	C(22)	-147.7(3)
C(6b)	C(6a)	C(6)	C(61)	145.6(3)	C(6b)	C(6a)	C(6)	C(62)	2.9(4)
C(6a')	C(6a)	C(6)	C(61)	-2.6(4)	C(6a')	C(6a)	C(6)	C(62)	-145.3(3)

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(3)	C(6b)	3.190(3)	2	O(3)	C(3a)	3.446(4)	2
N(6a')	C(5)	3.550(4)	55604				

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

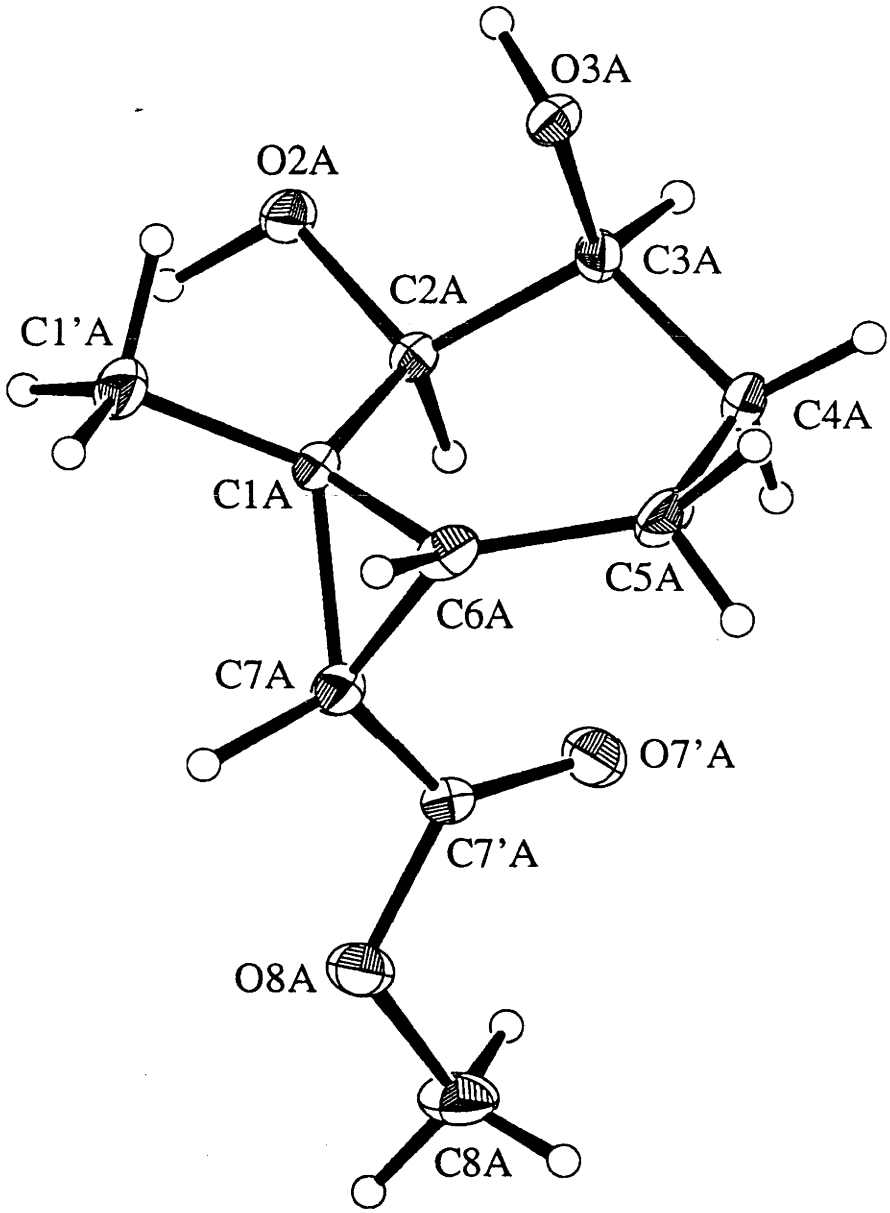
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	1/2-X,	-Y,	1/2+Z
(3)	1/2+X,	1/2-Y,	-Z	(4)	-X,	1/2+Y,	1/2-Z

1.4 X-Ray Structure Report for Compound 142*



* X-ray crystal data are presented as provided by Dr. David Hockless (Research School of Chemistry, ANU).

Experimental

Data Collection

A colorless prism crystal of $C_{10}H_{17}O_{4.50}$ having approximate dimensions of 0.24 x 0.22 x 0.16 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $25.10 < 2\theta < 99.43°$ corresponded to a C-centered monoclinic cell with dimensions:

$$a = 23.651(1)\ \AA$$
$$b = 6.458(2)\ \AA \qquad \beta = 114.089(5)°$$
$$c = 15.444(1)\ \AA$$
$$V = 2153.3(7)\ \AA^3$$

For Z = 8 and F.W. = 209.24, the calculated density is 1.29 g/cm^3. Based on the systematic absences of:

$$hkl: h+k \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

C2 (#5)

The data were collected at a temperature of -80 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.34° with a take-off angle of 6.0°. Scans of $(1.20 + 0.30 \tan \theta)°$ were made at a speed of 16.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 1839 reflections which were collected, 1765 were unique ($R_{int} = 0.072$). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 8.5 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.80 to 1.00. The data were corrected for Lorentz and

polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1631 observed reflections (I > 3.00σ(I)) and 260 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.036$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.056$$

The standard deviation of an observation of unit weight[4] was 2.34. The weighting scheme was based on counting statistics and included a factor (p = 0.033) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.21 and -0.15 $e^-/\mathring{A}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{10}H_{17}O_{4.50}$
Formula Weight	209.24
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.24 X 0.22 X 0.16 mm
Crystal System	monoclinic
Lattice Type	C-centered
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (25.1 - 99.4°)
Omega Scan Peak Width at Half-height	0.34°
Lattice Parameters	a = 23.651(1)Å b = 6.458(2) Å c = 15.444(1) Å β = 114.089(5)° V = 2153.3(7) Å^3
Space Group	C2 (#5)
Z value	8
D_{calc}	1.291 g/cm^3
F_{000}	904.00
μ(CuKα)	8.49 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R

Radiation	CuKα (λ = 1.54178 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-80.0°C
Scan Type	ω-2θ
Scan Rate	16.0°/min (in ω) (up to 4 scans)
Scan Width	(1.20 + 0.30 tan θ)°
$2\theta_{max}$	120.1°
No. of Reflections Measured	Total: 1839 Unique: 1765 (R_{int} = 0.072)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.8006 - 1.0000)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0330
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1631
No. Variables	260
Reflection/Parameter Ratio	6.27
Residuals: R; Rw	0.036 ; 0.056
Goodness of Fit Indicator	2.34

Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.21 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.15 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(01)	-0.2965(1)	0.1869	-0.4972(2)	3.21(6)
O(2A)	-0.4080(1)	-0.3896(5)	-0.4182(2)	3.06(6)
O(3A)	-0.3078(1)	-0.2292	-0.4551(2)	2.58(5)
O(7'A)	-0.2775(1)	-0.3058(7)	-0.1278(2)	4.72(8)
O(8A)	-0.3268(1)	-0.1004(6)	-0.0660(2)	3.84(7)
C(1A)	-0.3588(2)	-0.0850(7)	-0.3213(2)	2.54(7)
C(1'A)	-0.4155(2)	0.0285(8)	-0.3904(3)	3.91(9)
C(2A)	-0.3532(1)	-0.3138(7)	-0.3431(2)	2.45(7)
C(3A)	-0.2995(2)	-0.3478(7)	-0.3720(2)	2.51(8)
C(4A)	-0.2391(2)	-0.2839(8)	-0.2915(3)	3.34(9)
C(5A)	-0.2382(2)	-0.0545(9)	-0.2648(3)	3.69(9)
C(6A)	-0.2999(2)	0.0350(7)	-0.2777(3)	3.22(8)
C(7'A)	-0.3098(2)	-0.1583(7)	-0.1349(2)	2.89(8)
C(7A)	-0.3358(2)	-0.0147(7)	-0.2161(3)	3.09(8)
C(8A)	-0.3016(2)	-0.2252(9)	0.0199(3)	4.5(1)
C(1B)	-0.5742(1)	-0.3395(7)	-0.2541(2)	2.39(7)
C(1'B)	-0.6135(2)	-0.1516(7)	-0.2970(3)	3.56(9)
C(2B)	-0.5833(1)	-0.5278(6)	-0.3182(2)	2.30(7)
O(2B)	-0.6371(1)	-0.4929(5)	-0.4046(2)	2.73(5)
C(3B)	-0.5273(2)	-0.5661(8)	-0.3408(3)	3.20(8)
O(3B)	-0.5156(1)	-0.3914(7)	-0.3884(2)	3.73(6)
C(4B)	-0.4710(2)	-0.6048(9)	-0.2491(3)	3.9(1)
C(5B)	-0.4551(2)	-0.4214(9)	-0.1812(3)	4.1(1)
C(6B)	-0.5102(2)	-0.3036(8)	-0.1804(2)	3.12(8)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(7B)	-0.5591(2)	-0.3792(7)	-0.1476(3)	2.98(8)
C(7'B)	-0.5616(2)	-0.5889(8)	-0.1129(2)	2.83(8)
O(7'B)	-0.5380(1)	-0.7452(6)	-0.1266(2)	3.65(7)
C(8B)	-0.6072(2)	-0.7900(9)	-0.0298(3)	4.6(1)
O(8B)	-0.5959(1)	-0.5893(6)	-0.0611(2)	3.70(6)
H(01a)	-0.2618	0.1926	-0.5216	5.4194
H(01b)	-0.2964	0.0310	-0.4579	5.4194
H(1'Aa)	-0.4551	-0.0441	-0.3920	5.4194
H(1'Ab)	-0.4147	-0.0255	-0.4555	5.4194
H(1'Ac)	-0.4150	0.1839	-0.3789	5.4194
H(1'Ba)	-0.6018	-0.0423	-0.2519	4.2754
H(1'Bb)	-0.6558	-0.1847	-0.3146	4.2754
H(1'Bc)	-0.6075	-0.1094	-0.3516	4.2754
H(02B)	-0.6533	-0.6479	-0.4177	5.4194
H(02A)	-0.4455	-0.3884	-0.3957	5.4194
H(2A)	-0.3481	-0.4177	-0.2799	5.4194
H(2B)	-0.5983	-0.6761	-0.2881	5.4194
H(3B)	-0.5359	-0.7175	-0.3832	5.4194
H(03A)	-0.3370	-0.2959	-0.5030	5.4194
H(3A)	-0.2935	-0.5279	-0.3754	5.4194
H(03B)	-0.5494	-0.4071	-0.4509	5.4194
H(4Bb)	-0.4789	-0.7217	-0.2185	4.6338
H(4Aa)	-0.2016	-0.2957	-0.3100	5.4194
H(4Ab)	-0.2315	-0.3512	-0.2342	5.4194

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(4Ba)	-0.4366	-0.6327	-0.2640	4.6338
H(5Bb)	-0.4300	-0.4697	-0.1214	5.4194
H(5Ab)	-0.2081	-0.0335	-0.2092	5.4194
H(5Aa)	-0.2076	-0.0190	-0.2950	5.4194
H(5Ba)	-0.4341	-0.3451	-0.2235	5.4194
H(6B)	-0.4959	-0.1329	-0.1656	5.4194
H(6A)	-0.3052	0.2076	-0.2924	5.4194
H(7B)	-0.5798	-0.2769	-0.1055	5.4194
H(7A)	-0.3642	0.1225	-0.2047	5.4194
H(8Bc)	-0.5691	-0.8473	0.0134	5.5225
H(8Ba)	-0.6346	-0.7753	0.0008	5.5225
H(8Bb)	-0.6252	-0.8791	-0.0830	5.5225
H(8Ab)	-0.3259	-0.2056	0.0553	5.4032
H(8Ac)	-0.2601	-0.1843	0.0570	5.4032
H(8Aa)	-0.3024	-0.3672	0.0033	5.4032

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(01)	0.035(1)	0.040(1)	0.047(2)	0.006(1)	0.017(1)	0.008(1)
O(2A)	0.027(1)	0.052(2)	0.036(1)	-0.010(1)	0.012(1)	-0.007(1)
O(3A)	0.028(1)	0.038(1)	0.027(1)	-0.004(1)	0.007(1)	0.001(1)
O(7'A)	0.070(2)	0.070(2)	0.041(2)	0.035(2)	0.024(2)	0.013(2)
O(8A)	0.061(2)	0.050(2)	0.036(1)	0.011(2)	0.021(1)	-0.001(1)
C(1A)	0.027(2)	0.038(2)	0.025(2)	0.006(2)	0.005(1)	-0.001(2)
C(1'A)	0.043(2)	0.049(3)	0.042(2)	0.017(2)	0.004(2)	0.000(2)
C(2A)	0.024(2)	0.036(2)	0.029(2)	-0.001(2)	0.007(1)	-0.004(2)
C(3A)	0.029(2)	0.034(2)	0.032(2)	0.006(2)	0.012(1)	0.004(2)
C(4A)	0.023(2)	0.063(3)	0.034(2)	0.007(2)	0.004(2)	0.001(2)
C(5A)	0.026(2)	0.067(3)	0.036(2)	-0.010(2)	0.001(2)	-0.005(2)
C(6A)	0.046(2)	0.035(2)	0.032(2)	-0.001(2)	0.006(2)	0.000(2)
C(7'A)	0.035(2)	0.043(2)	0.027(2)	0.002(2)	0.009(2)	-0.006(2)
C(7A)	0.038(2)	0.041(2)	0.031(2)	0.009(2)	0.007(2)	-0.001(2)
C(8A)	0.082(3)	0.059(3)	0.032(2)	0.006(3)	0.025(2)	0.003(2)
C(1B)	0.027(2)	0.032(2)	0.030(2)	-0.002(2)	0.010(1)	-0.006(2)
C(1'B)	0.054(2)	0.034(2)	0.039(2)	0.003(2)	0.010(2)	0.004(2)
C(2B)	0.023(2)	0.033(2)	0.026(2)	0.002(2)	0.004(1)	-0.001(2)
O(2B)	0.028(1)	0.036(1)	0.030(1)	-0.003(1)	0.002(1)	0.005(1)
C(3B)	0.032(2)	0.054(2)	0.036(2)	0.005(2)	0.014(2)	-0.002(2)
O(3B)	0.028(1)	0.078(2)	0.033(1)	-0.007(1)	0.010(1)	0.006(2)
C(4B)	0.031(2)	0.074(3)	0.044(2)	0.014(2)	0.017(2)	0.006(2)
C(5B)	0.029(2)	0.084(4)	0.035(2)	-0.007(2)	0.004(2)	0.007(2)
C(6B)	0.033(2)	0.048(2)	0.031(2)	-0.010(2)	0.008(2)	0.001(2)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(7B)	0.044(2)	0.039(2)	0.030(2)	-0.007(2)	0.016(2)	-0.001(2)
C(7'B)	0.028(2)	0.053(3)	0.020(2)	-0.004(2)	0.003(1)	-0.002(2)
O(7'B)	0.056(2)	0.040(2)	0.039(2)	0.008(1)	0.015(1)	0.005(1)
C(8B)	0.052(3)	0.068(3)	0.047(2)	-0.020(3)	0.011(2)	0.012(3)
O(8B)	0.041(1)	0.061(2)	0.039(1)	-0.007(2)	0.016(1)	0.004(2)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(2A)	C(2A)	1.427(4)	O(3A)	C(3A)	1.438(4)
O(7'A)	C(7'A)	1.197(5)	O(8A)	C(7'A)	1.335(5)
O(8A)	C(8A)	1.456(5)	C(1A)	C(1'A)	1.519(5)
C(1A)	C(2A)	1.533(6)	C(1A)	C(6A)	1.493(5)
C(1A)	C(7A)	1.557(5)	C(2A)	C(3A)	1.524(5)
C(3A)	C(4A)	1.519(5)	C(4A)	C(5A)	1.536(7)
C(5A)	C(6A)	1.505(6)	C(6A)	C(7A)	1.546(6)
C(7'A)	C(7A)	1.476(6)	C(1B)	C(1'B)	1.507(5)
C(1B)	C(2B)	1.527(5)	C(1B)	C(6B)	1.496(5)
C(1B)	C(7B)	1.555(5)	C(2B)	O(2B)	1.437(4)
C(2B)	C(3B)	1.519(5)	C(3B)	O(3B)	1.435(6)
C(3B)	C(4B)	1.517(5)	C(4B)	C(5B)	1.523(7)
C(5B)	C(6B)	1.513(6)	C(6B)	C(7B)	1.521(5)
C(7B)	C(7'B)	1.466(6)	C(7'B)	O(7'B)	1.212(5)
C(7'B)	O(8B)	1.354(4)	C(8B)	O(8B)	1.445(6)

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(01)	H(01a)	1.03	O(01)	H(01b)	1.18
O(2A)	H(02A)	1.08	O(3A)	H(03A)	0.89
C(1'A)	H(1'Aa	1.04	C(1'A)	H(1'Ab	1.07
C(1'A)	H(1'Ac	1.02	C(2A)	H(2A)	1.15
C(3A)	H(3A)	1.17	C(4A)	H(4Aa)	1.04
C(4A)	H(4Ab)	0.94	C(5A)	H(5Ab)	0.87
C(5A)	H(5Aa)	1.03	C(6A)	H(6A)	1.13
C(7A)	H(7A)	1.17	C(8A)	H(8Ab)	0.95
C(8A)	H(8Ac)	0.95	C(8A)	H(8Aa)	0.95
C(1'B)	H(1'Ba	0.95	C(1'B)	H(1'Bb	0.95
C(1'B)	H(1'Bc	0.95	C(2B)	H(2B)	1.18
O(2B)	H(02B)	1.06	C(3B)	H(3B)	1.15
O(3B)	H(03B)	0.98	C(4B)	H(4Bb)	0.95
C(4B)	H(4Ba)	0.95	C(5B)	H(5Bb)	0.92
C(5B)	H(5Ba)	1.09	C(6B)	H(6B)	1.15
C(7B)	H(7B)	1.17	C(8B)	H(8Bc)	0.95
C(8B)	H(8Ba)	0.95	C(8B)	H(8Bb)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(7'A)	O(8A)	C(8A)	115.3(3)	C(1'A)	C(1A)	C(2A)	116.2(3)
C(1'A)	C(1A)	C(6A)	117.4(4)	C(1'A)	C(1A)	C(7A)	115.1(3)
C(2A)	C(1A)	C(6A)	116.9(3)	C(2A)	C(1A)	C(7A)	119.0(3)
C(6A)	C(1A)	C(7A)	60.9(2)	O(2A)	C(2A)	C(1A)	112.2(3)
O(2A)	C(2A)	C(3A)	107.5(3)	C(1A)	C(2A)	C(3A)	111.0(3)
O(3A)	C(3A)	C(2A)	111.0(3)	O(3A)	C(3A)	C(4A)	109.0(3)
C(2A)	C(3A)	C(4A)	109.9(3)	C(3A)	C(4A)	C(5A)	112.7(3)
C(4A)	C(5A)	C(6A)	115.4(4)	C(1A)	C(6A)	C(5A)	122.4(4)
C(1A)	C(6A)	C(7A)	61.6(3)	C(5A)	C(6A)	C(7A)	125.8(4)
O(7'A)	C(7'A)	O(8A)	122.5(4)	O(7'A)	C(7'A)	C(7A)	127.4(4)
O(8A)	C(7'A)	C(7A)	110.1(3)	C(1A)	C(7A)	C(6A)	57.5(2)
C(1A)	C(7A)	C(7'A)	123.4(4)	C(6A)	C(7A)	C(7'A)	120.7(3)
C(1'B)	C(1B)	C(2B)	117.2(3)	C(1'B)	C(1B)	C(6B)	117.4(3)
C(1'B)	C(1B)	C(7B)	115.6(3)	C(2B)	C(1B)	C(6B)	116.6(3)
C(2B)	C(1B)	C(7B)	117.7(3)	C(6B)	C(1B)	C(7B)	59.8(2)
C(1B)	C(2B)	O(2B)	108.3(3)	C(1B)	C(2B)	C(3B)	111.9(3)
O(2B)	C(2B)	C(3B)	109.8(3)	C(2B)	C(3B)	O(3B)	111.0(3)
C(2B)	C(3B)	C(4B)	109.2(3)	O(3B)	C(3B)	C(4B)	109.1(3)
C(3B)	C(4B)	C(5B)	113.0(4)	C(4B)	C(5B)	C(6B)	115.1(3)
C(1B)	C(6B)	C(5B)	121.6(4)	C(1B)	C(6B)	C(7B)	62.1(2)
C(5B)	C(6B)	C(7B)	128.1(4)	C(1B)	C(7B)	C(6B)	58.2(2)
C(1B)	C(7B)	C(7'B)	120.8(3)	C(6B)	C(7B)	C(7'B)	124.6(4)
C(7B)	C(7'B)	O(7'B)	128.0(3)	C(7B)	C(7'B)	O(8B)	109.9(4)
O(7'B)	C(7'B)	O(8B)	122.0(4)	C(7'B)	O(8B)	C(8B)	115.9(4)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
H(01a)	O(01)	H(01b)	112.5	C(2A)	O(2A)	H(02A)	109.3
C(3A)	O(3A)	H(03A)	105.2	C(1A)	C(1'A)	H(1'Aa	109.2
C(1A)	C(1'A)	H(1'Ab	98.8	C(1A)	C(1'A)	H(1'Ac	114.2
H(1'Aa	C(1'A)	H(1'Ab	101.0	H(1'Aa	C(1'A)	H(1'Ac	113.3
H(1'Ab	C(1'A)	H(1'Ac	118.7	O(2A)	C(2A)	H(2A)	103.7
C(1A)	C(2A)	H(2A)	111.5	C(3A)	C(2A)	H(2A)	110.6
O(3A)	C(3A)	H(3A)	117.5	C(2A)	C(3A)	H(3A)	106.6
C(4A)	C(3A)	H(3A)	102.4	C(3A)	C(4A)	H(4Aa)	112.3
C(3A)	C(4A)	H(4Ab)	113.6	C(5A)	C(4A)	H(4Aa)	103.0
C(5A)	C(4A)	H(4Ab)	102.6	H(4Aa)	C(4A)	H(4Ab)	111.8
C(4A)	C(5A)	H(5Ab)	109.2	C(4A)	C(5A)	H(5Aa)	91.6
C(6A)	C(5A)	H(5Ab)	115.3	C(6A)	C(5A)	H(5Aa)	132.4
H(5Ab)	C(5A)	H(5Aa)	88.2	C(1A)	C(6A)	H(6A)	114.4
C(5A)	C(6A)	H(6A)	115.2	C(7A)	C(6A)	H(6A)	106.5
C(1A)	C(7A)	H(7A)	113.6	C(6A)	C(7A)	H(7A)	115.4
C(7'A)	C(7A)	H(7A)	114.5	O(8A)	C(8A)	H(8Ab)	109.5
O(8A)	C(8A)	H(8Ac)	109.5	O(8A)	C(8A)	H(8Aa)	109.5
H(8Ab)	C(8A)	H(8Ac)	109.5	H(8Ab)	C(8A)	H(8Aa)	109.5
H(8Ac)	C(8A)	H(8Aa)	109.5	C(1B)	C(1'B)	H(1'Ba	109.5
C(1B)	C(1'B)	H(1'Bb	109.5	C(1B)	C(1'B)	H(1'Bc	109.5
H(1'Ba	C(1'B)	H(1'Bb	109.5	H(1'Ba	C(1'B)	H(1'Bc	109.5
H(1'Bb	C(1'B)	H(1'Bc	109.5	C(1B)	C(2B)	H(2B)	112.0
O(2B)	C(2B)	H(2B)	101.4	C(3B)	C(2B)	H(2B)	112.9
C(2B)	O(2B)	H(02B)	98.2	C(2B)	C(3B)	H(3B)	107.6

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
O(3B)	C(3B)	H(3B)	113.7	C(4B)	C(3B)	H(3B)	106.0
C(3B)	O(3B)	H(03B)	100.0	C(3B)	C(4B)	H(4Bb)	108.6
C(3B)	C(4B)	H(4Ba)	108.6	C(5B)	C(4B)	H(4Bb)	108.6
C(5B)	C(4B)	H(4Ba)	108.6	H(4Bb)	C(4B)	H(4Ba)	109.5
C(4B)	C(5B)	H(5Bb)	107.6	C(4B)	C(5B)	H(5Ba)	89.1
C(6B)	C(5B)	H(5Bb)	111.4	C(6B)	C(5B)	H(5Ba)	112.5
H(5Bb)	C(5B)	H(5Ba)	119.3	C(1B)	C(6B)	H(6B)	115.1
C(5B)	C(6B)	H(6B)	107.4	C(7B)	C(6B)	H(6B)	116.4
C(1B)	C(7B)	H(7B)	121.9	C(6B)	C(7B)	H(7B)	123.6
C(7'B)	C(7B)	H(7B)	103.4	O(8B)	C(8B)	H(8Bc)	109.5
O(8B)	C(8B)	H(8Ba)	109.5	O(8B)	C(8B)	H(8Bb)	109.5
H(8Bc)	C(8B)	H(8Ba)	109.5	H(8Bc)	C(8B)	H(8Bb)	109.5
H(8Ba)	C(8B)	H(8Bb)	109.5				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(2A)	C(2A)	C(1A)	C(1'A)	-8.7(5)	O(2A)	C(2A)	C(1A)	C(6A)	-154.3(3)
O(2A)	C(2A)	C(1A)	C(7A)	135.7(3)	O(2A)	C(2A)	C(3A)	O(3A)	63.4(4)
O(2A)	C(2A)	C(3A)	C(4A)	-176.0(3)	O(3A)	C(3A)	C(2A)	C(1A)	-59.7(4)
O(3A)	C(3A)	C(4A)	C(5A)	61.4(4)	O(7'A)	C(7'A)	O(8A)	C(8A)	2.0(6)
O(7'A)	C(7'A)	C(7A)	C(1A)	36.6(6)	O(7'A)	C(7'A)	C(7A)	C(6A)	-32.5(6)
O(8A)	C(7'A)	C(7A)	C(1A)	-144.0(3)	O(8A)	C(7'A)	C(7A)	C(6A)	146.9(4)
C(1A)	C(2A)	C(3A)	C(4A)	60.9(4)	C(1A)	C(6A)	C(5A)	C(4A)	-5.1(5)
C(1A)	C(6A)	C(7A)	C(7'A)	112.4(4)	C(1A)	C(7A)	C(6A)	C(5A)	-111.2(5)
C(1'A)	C(1A)	C(2A)	C(3A)	111.6(4)	C(1'A)	C(1A)	C(6A)	C(5A)	-138.6(4)
C(1'A)	C(1A)	C(6A)	C(7A)	105.0(4)	C(1'A)	C(1A)	C(7A)	C(6A)	-108.7(4)
C(1'A)	C(1A)	C(7A)	C(7'A)	143.6(4)	C(2A)	C(1A)	C(6A)	C(5A)	6.5(5)
C(2A)	C(1A)	C(6A)	C(7A)	-109.9(4)	C(2A)	C(1A)	C(7A)	C(6A)	106.4(4)
C(2A)	C(1A)	C(7A)	C(7'A)	-1.3(5)	C(2A)	C(3A)	C(4A)	C(5A)	-60.4(4)
C(3A)	C(2A)	C(1A)	C(6A)	-33.9(4)	C(3A)	C(2A)	C(1A)	C(7A)	-103.9(3)
C(3A)	C(4A)	C(5A)	C(6A)	31.8(5)	C(4A)	C(5A)	C(6A)	C(7A)	71.2(5)
C(5A)	C(6A)	C(1A)	C(7A)	116.4(4)	C(5A)	C(6A)	C(7A)	C(7'A)	1.3(6)
C(6A)	C(1A)	C(7A)	C(7'A)	-107.7(4)	C(7A)	C(7'A)	O(8A)	C(8A)	-177.4(3)
C(1B)	C(2B)	C(3B)	O(3B)	-60.0(4)	C(1B)	C(2B)	C(3B)	C(4B)	60.3(5)
C(1B)	C(6B)	C(5B)	C(4B)	-11.5(6)	C(1B)	C(6B)	C(7B)	C(7'B)	107.8(4)
C(1B)	C(7B)	C(6B)	C(5B)	-109.8(4)	C(1B)	C(7B)	C(7'B)	O(7'B)	49.6(6)
C(1B)	C(7B)	C(7'B)	O(8B)	-129.8(3)	C(1'B)	C(1B)	C(2B)	O(2B)	-10.0(4)
C(1'B)	C(1B)	C(2B)	C(3B)	111.1(4)	C(1'B)	C(1B)	C(6B)	C(5B)	-135.3(4)
C(1'B)	C(1B)	C(6B)	C(7B)	105.1(4)	C(1'B)	C(1B)	C(7B)	C(6B)	-108.2(4)
C(1'B)	C(1B)	C(7B)	C(7'B)	137.8(4)	C(2B)	C(1B)	C(6B)	C(5B)	11.4(5)

Table 7. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(2B)	C(1B)	C(6B)	C(7B)	-108.1(4)	C(2B)	C(1B)	C(7B)	C(6B)	106.2(4)
C(2B)	C(1B)	C(7B)	C(7'B)	-7.8(5)	C(2B)	C(3B)	C(4B)	C(5B)	-61.2(5)
O(2B)	C(2B)	C(1B)	C(6B)	-156.8(3)	O(2B)	C(2B)	C(1B)	C(7B)	135.1(3)
O(2B)	C(2B)	C(3B)	O(3B)	60.2(4)	O(2B)	C(2B)	C(3B)	C(4B)	-179.5(4)
C(3B)	C(2B)	C(1B)	C(6B)	-35.7(4)	C(3B)	C(2B)	C(1B)	C(7B)	-103.8(4)
C(3B)	C(4B)	C(5B)	C(6B)	36.3(5)	O(3B)	C(3B)	C(4B)	C(5B)	60.3(4)
C(4B)	C(5B)	C(6B)	C(7B)	66.0(5)	C(5B)	C(6B)	C(1B)	C(7B)	119.5(5)
C(5B)	C(6B)	C(7B)	C(7'B)	-2.0(6)	C(6B)	C(1B)	C(7B)	C(7'B)	-114.0(4)
C(6B)	C(7B)	C(7'B)	O(7'B)	-20.8(6)	C(6B)	C(7B)	C(7'B)	O(8B)	159.8(3)
C(7B)	C(7'B)	O(8B)	C(8B)	174.4(3)	O(7'B)	C(7'B)	O(8B)	C(8B)	-5.1(5)

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(01)	O(2B)	2.664(3)	46402	O(01)	O(3A)	2.8032(9)	1
O(01)	O(3A)	2.901(3)	45404	O(01)	C(6A)	3.560(5)	1
O(01)	C(3A)	3.589(4)	56501	O(2A)	O(3B)	2.763(3)	1
O(2A)	O(3B)	2.790(4)	45402	O(2A)	O(2B)	3.386(4)	45402
O(2A)	C(3B)	3.585(5)	45402	O(3A)	O(2B)	2.643(3)	45402
O(3A)	C(1'B)	3.543(5)	45402	O(7'A)	C(8A)	3.328(6)	44504
O(7'A)	O(8A)	3.555(4)	44504	O(8A)	C(8B)	3.246(5)	46502
O(8A)	C(5B)	3.502(5)	1	C(3A)	O(2B)	3.288(4)	45402
C(5A)	O(8B)	3.554(4)	3	C(8A)	C(8B)	3.584(7)	46502
C(5B)	O(8B)	3.599(5)	45502	C(7'B)	C(7'B)	3.515(6)	45502
C(7'B)	O(8B)	3.595(4)	45502	O(7'B)	C(8B)	3.307(5)	45502
O(7'B)	O(8B)	3.457(4)	45502	O(7'B)	O(7'B)	3.574(5)	45502

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

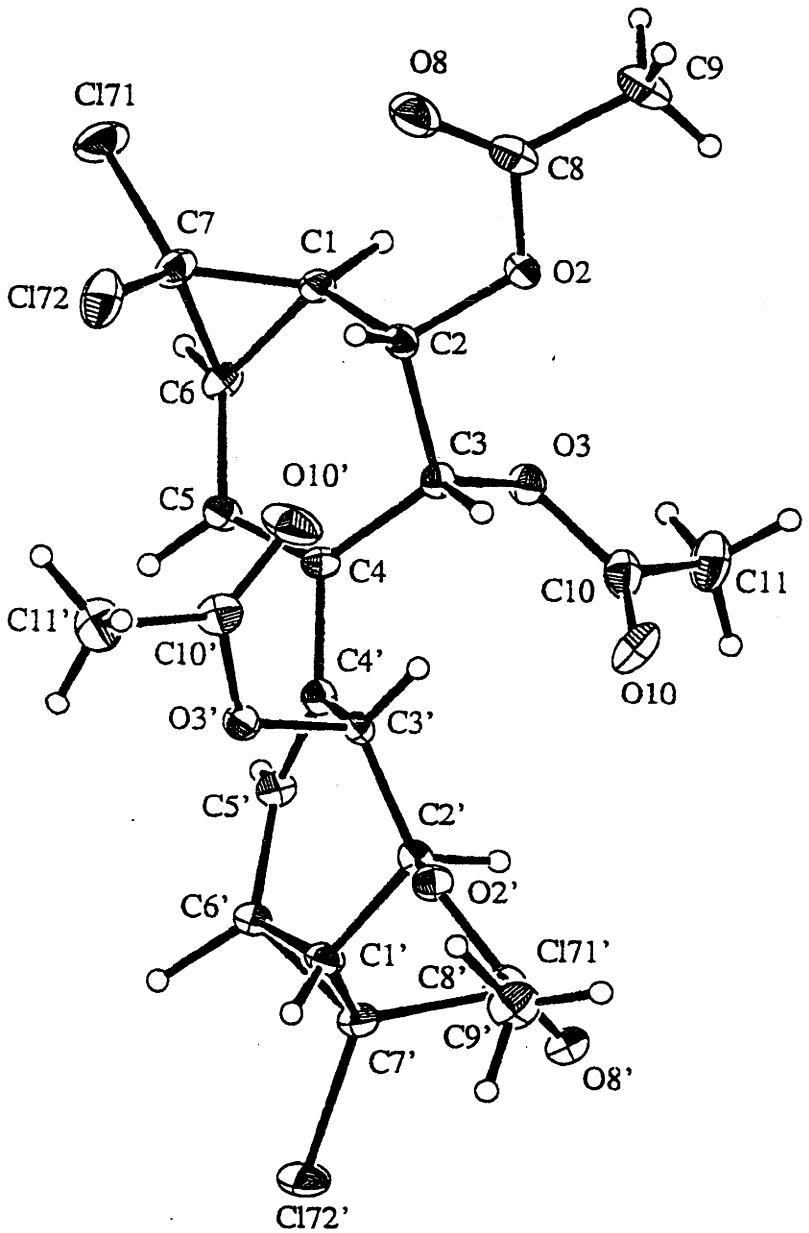
For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z		(2)	-X,	Y,	-Z

1.5 X-Ray Structure Report for Compound 209*



* X-ray crystal data are presented as provided by Dr. David Hockless (Research School of Chemistry, ANU).

Experimental

Data Collection

A colorless prism crystal of $C_{22}H_{22}Cl_4O_8$ having approximate dimensions of 0.34 x 0.28 x 0.18 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6R diffractometer with graphite monochromated Mo-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection , obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $9.19 < 2\theta < 26.33°$ corresponded to a primitive monoclinic cell with dimensions:

$$a = 7.854(3)\ \AA$$
$$b = 13.794(1)\ \AA \qquad \beta = 92.95(2)°$$
$$c = 12.147(2)\ \AA$$
$$V = 1314.3(5)\ \AA^3$$

For Z = 2 and F.W. = 556.22, the calculated density is 1.41 g/cm^3. Based on the systematic absences of:

$$0k0:\ k \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$P2_1\ (\#4)$$

The data were collected at a temperature of -60 $\pm$ 1°C using the ω-2θ scan technique to a maximum 2θ value of 60.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take-off angle of 6.0°. Scans of $(0.89 + 0.30 \tan \theta)°$ were made at a speed of 4.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm, the crystal to detector distance was 400 mm, and the detector aperture was 7.0 x 7.0 mm (horizontal x vertical).

Data Reduction

Of the 4260 reflections which were collected, 4001 were unique ($R_{int} = 0.038$). The intensities of three representative reflection were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo-Kα radiation is 4.9 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.94 to 1.00. The data were corrected for Lorentz and

polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1803 observed reflections (I $> 3.00\sigma(I)$) and 305 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.041$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.035$$

The standard deviation of an observation of unit weight[4] was 1.60. The weighting scheme was based on counting statistics and included a factor (p = 0.010) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and -0.20 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

where w = $\frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$

$\sigma_c(Fo)$ = e.s.d. based on counting statistics

p = p-factor

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{22}H_{22}Cl_4O_8$
Formula Weight	556.22
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.34 X 0.28 X 0.18 mm
Crystal System	monoclinic
Lattice Type	Primitive
No. of Reflections Used for Unit	
Cell Determination (2θ range)	25 (9.2 - 26.3°)
Omega Scan Peak Width	
at Half-height	0.32°
Lattice Parameters	a = 7.854(3)Å b = 13.794(1) Å c = 12.147(2) Å β = 92.95(2)°
	V = 1314.3(5) Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.405 g/cm^3
F_{000}	572.00
μ(MoKα)	4.92 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6R

Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Take-off Angle	6.0°
Detector Aperture	7.0 mm horizontal 7.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-60.0°C
Scan Type	ω-2θ
Scan Rate	4.0°/min (in ω) (up to 4 scans)
Scan Width	(0.89 + 0.30 tan θ)°
$2\theta_{max}$	60.0°
No. of Reflections Measured	Total: 4260 Unique: 4001 (R_{int} = 0.038)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.9397 - 1.0000)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1803
No. Variables	305
Reflection/Parameter Ratio	5.91
Residuals: R; Rw	0.041 ; 0.035
Goodness of Fit Indicator	1.60

Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.24 $e^-/\AA^3$
Minimum peak in Final Diff. Map	-0.20 $e^-/\AA^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Cl(71)	-0.9519(2)	0.2464	-0.3050(2)	5.77(5)
Cl(71')	-0.1135(2)	-0.2797(2)	-0.3683(1)	4.38(4)
Cl(72)	-0.6970(2)	0.1969(2)	-0.1316(1)	5.25(5)
Cl(72')	-0.1694(3)	-0.4234	-0.1973(2)	5.21(5)
O(2)	-0.3498(5)	0.2629(3)	-0.3900(3)	3.2(1)
O(2')	0.0693(5)	-0.1106(3)	-0.0835(3)	3.0(1)
O(3)	-0.3491(5)	0.0779(3)	-0.4562(3)	3.0(1)
O(3')	-0.2441(5)	-0.0415(3)	-0.0508(3)	2.8(1)
O(8')	0.2385(6)	-0.2177(3)	-0.1634(4)	3.7(1)
O(8)	-0.4460(8)	0.3833(4)	-0.2858(5)	5.5(2)
O(10)	-0.0950(6)	0.0040(4)	-0.4299(4)	5.0(1)
O(10')	-0.2463(9)	0.1205(4)	-0.0654(4)	6.3(2)
C(1)	-0.6260(7)	0.1933(4)	-0.3567(5)	2.6(1)
C(1')	-0.1451(8)	-0.2291(4)	-0.1431(5)	2.8(1)
C(2)	-0.4376(8)	0.1937(5)	-0.3236(5)	2.6(1)
C(2')	-0.0627(7)	-0.1308(5)	-0.1671(5)	2.5(1)
C(3)	-0.3505(7)	0.0965(4)	-0.3388(5)	2.4(1)
C(3')	-0.1910(7)	-0.0491(4)	-0.1633(5)	2.3(1)
C(4)	-0.4451(8)	0.0150(4)	-0.2843(5)	2.3(1)
C(4')	-0.3482(7)	-0.0679(5)	-0.2375(5)	2.6(1)
C(5)	-0.6149(8)	0.0185(4)	-0.2842(5)	2.8(1)
C(5')	-0.4039(8)	-0.1601(5)	-0.2527(5)	3.0(2)
C(6)	-0.7186(7)	0.0969(5)	-0.3360(5)	2.9(1)
C(6')	-0.3271(8)	-0.2432(4)	-0.1911(5)	3.3(1)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
C(7)	-0.7558(7)	0.1903(5)	-0.2723(5)	3.6(2)
C(7')	-0.1809(8)	-0.2996(5)	-0.2353(5)	3.6(2)
C(8)	-0.370(1)	0.3577(5)	-0.3624(6)	3.9(2)
C(8')	0.2148(8)	-0.1620(5)	-0.0898(6)	3.0(2)
C(9)	-0.283(1)	0.4222(6)	-0.4432(6)	5.0(2)
C(9')	0.3384(9)	-0.1396(6)	0.0043(6)	4.5(2)
C(10)	-0.210(1)	0.0305(5)	-0.4906(6)	4.0(2)
C(10')	-0.2652(9)	0.0497(5)	-0.0108(6)	3.4(2)
C(11)	-0.222(1)	0.0216(6)	-0.6142(6)	5.1(2)
C(11')	-0.314(1)	0.0458(5)	0.1063(6)	5.1(2)
H(1)	-0.6494	0.2115	-0.4504	6.0847
H(1')	-0.0873	-0.2505	-0.0645	6.0847
H(2)	-0.4233	0.2122	-0.2484	3.0931
H(2')	-0.0152	-0.1325	-0.2374	3.0194
H(3)	-0.2368	0.0995	-0.3084	2.8358
H(3')	-0.1392	0.0100	-0.1841	2.8021
H(5)	-0.6723	-0.0324	-0.2487	3.3746
H(5')	-0.4957	-0.1720	-0.3050	3.6002
H(6)	-0.8424	0.0924	-0.3813	6.0847
H(6')	-0.3999	-0.3039	-0.1428	6.0847
H(9c)	-0.2110	0.3841	-0.4864	6.0206
H(9a)	-0.3668	0.4534	-0.4900	6.0206
H(9b)	-0.2166	0.4697	-0.4039	6.0206
H(9'a)	0.2876	-0.0959	0.0533	5.4132

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(9'b)	0.4379	-0.1110	-0.0229	5.4132
H(9'c)	0.3685	-0.1978	0.0424	5.4132
H(11c)	-0.1875	-0.0416	-0.6348	6.1706
H(11a)	-0.3365	0.0324	-0.6407	6.1706
H(11b)	-0.1498	0.0684	-0.6453	6.1706
H(11'a)	-0.4185	0.0797	0.1133	6.1480
H(11'b)	-0.2275	0.0751	0.1524	6.1480
H(11'c)	-0.3281	-0.0199	0.1277	6.1480

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(71)	0.0332(9)	0.050(1)	0.136(2)	0.0100(9)	0.007(1)	0.003(1)
Cl(71')	0.068(1)	0.052(1)	0.047(1)	0.004(1)	0.0058(9)	-0.0131(9)
Cl(72)	0.064(1)	0.086(2)	0.051(1)	-0.006(1)	0.019(1)	-0.020(1)
Cl(72')	0.075(1)	0.0264(8)	0.098(2)	0.003(1)	0.014(1)	0.001(1)
O(2)	0.038(3)	0.035(2)	0.047(3)	0.000(2)	0.008(2)	0.011(2)
O(2')	0.036(3)	0.037(2)	0.040(3)	0.002(2)	-0.004(2)	0.000(2)
O(3)	0.043(3)	0.044(2)	0.028(2)	0.000(2)	0.002(2)	0.000(2)
O(3')	0.045(3)	0.031(2)	0.032(2)	0.001(2)	0.006(2)	-0.001(2)
O(8')	0.045(3)	0.041(3)	0.054(3)	0.010(2)	0.005(2)	-0.002(3)
O(8)	0.103(5)	0.039(3)	0.069(4)	-0.004(3)	0.021(4)	0.001(3)
O(10)	0.044(3)	0.081(4)	0.063(4)	0.020(3)	0.007(3)	-0.021(3)
O(10')	0.157(6)	0.031(3)	0.053(4)	0.005(3)	0.020(4)	-0.001(3)
C(1)	0.025(3)	0.033(3)	0.039(4)	0.003(3)	-0.001(3)	0.004(3)
C(1')	0.039(4)	0.025(3)	0.043(4)	-0.001(3)	0.002(3)	0.003(3)
C(2)	0.038(4)	0.032(3)	0.028(3)	0.001(3)	0.001(3)	0.003(3)
C(2')	0.031(3)	0.035(3)	0.029(3)	-0.004(3)	-0.004(3)	0.002(3)
C(3)	0.022(3)	0.038(4)	0.029(4)	0.001(3)	-0.004(3)	0.003(3)
C(3')	0.032(4)	0.026(3)	0.031(3)	-0.003(3)	0.005(3)	0.002(3)
C(4)	0.032(4)	0.025(3)	0.031(4)	0.000(3)	-0.004(3)	-0.003(3)
C(4')	0.029(3)	0.036(3)	0.032(4)	-0.002(3)	0.000(3)	0.000(3)
C(5)	0.035(4)	0.032(4)	0.039(4)	-0.002(3)	-0.001(3)	0.004(3)
C(5')	0.038(4)	0.035(4)	0.041(4)	0.003(3)	0.000(3)	-0.002(3)
C(6)	0.020(3)	0.047(4)	0.043(4)	0.006(3)	-0.008(3)	-0.001(3)
C(6')	0.044(4)	0.027(3)	0.053(4)	0.002(3)	0.012(3)	0.004(3)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(7)	0.029(3)	0.043(4)	0.064(4)	0.006(3)	-0.001(3)	-0.004(4)
C(7')	0.045(4)	0.032(3)	0.061(4)	0.005(3)	0.009(3)	0.001(4)
C(8)	0.051(5)	0.038(4)	0.057(5)	-0.005(4)	-0.012(4)	0.013(4)
C(8')	0.031(4)	0.038(4)	0.045(4)	-0.002(3)	0.000(3)	0.017(3)
C(9)	0.072(6)	0.046(4)	0.071(6)	-0.009(4)	-0.009(5)	0.023(4)
C(9')	0.051(5)	0.069(5)	0.050(5)	0.007(4)	-0.013(4)	0.002(4)
C(10)	0.056(5)	0.049(4)	0.048(5)	-0.014(4)	0.018(4)	-0.011(4)
C(10')	0.050(4)	0.043(4)	0.036(4)	0.002(4)	-0.005(3)	-0.010(4)
C(11)	0.062(5)	0.088(6)	0.047(5)	-0.012(5)	0.020(4)	-0.022(5)
C(11')	0.092(7)	0.057(5)	0.047(5)	-0.011(5)	0.019(4)	-0.020(4)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
Cl(71)	C(7)	1.752(6)	Cl(71')	C(7')	1.748(6)
Cl(72)	C(7)	1.749(7)	Cl(72')	C(7')	1.770(7)
O(2)	C(2)	1.447(7)	O(2)	C(8)	1.361(8)
O(2')	C(2')	1.440(7)	O(2')	C(8')	1.350(7)
O(3)	C(3)	1.450(7)	O(3)	C(10)	1.356(8)
O(3')	C(3')	1.453(6)	O(3')	C(10')	1.362(7)
O(8')	C(8')	1.200(7)	O(8)	C(8)	1.187(9)
O(10)	C(10)	1.195(8)	O(10')	C(10')	1.194(8)
C(1)	C(2)	1.513(7)	C(1)	C(6)	1.541(8)
C(1)	C(7)	1.483(8)	C(1')	C(2')	1.537(8)
C(1')	C(6')	1.528(8)	C(1')	C(7')	1.499(8)
C(2)	C(3)	1.520(8)	C(2')	C(3')	1.515(8)
C(3)	C(4)	1.518(8)	C(3')	C(4')	1.514(8)
C(4)	C(4')	1.472(8)	C(4)	C(5)	1.334(8)
C(4')	C(5')	1.355(8)	C(5)	C(6)	1.476(8)
C(5')	C(6')	1.479(8)	C(6)	C(7)	1.538(9)
C(6')	C(7')	1.509(8)	C(8)	C(9)	1.51(1)
C(8')	C(9')	1.494(9)	C(10)	C(11)	1.505(9)
C(10')	C(11')	1.493(9)			

Table 4. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
C(1)	H(1)	1.17	C(1')	H(1')	1.08
C(2)	H(2)	0.95	C(2')	H(2')	0.95
C(3)	H(3)	0.95	C(3')	H(3')	0.95
C(5)	H(5)	0.95	C(5')	H(5')	0.95
C(6)	H(6)	1.09	C(6')	H(6')	1.19
C(9)	H(9c)	0.95	C(9)	H(9a)	0.95
C(9)	H(9b)	0.95	C(9')	H(9'a)	0.95
C(9')	H(9'b)	0.95	C(9')	H(9'c)	0.95
C(11)	H(11c)	0.95	C(11)	H(11a)	0.95
C(11)	H(11b)	0.95	C(11')	H(11'a	0.95
C(11')	H(11'b	0.95	C(11')	H(11'c	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	O(2)	C(8)	115.6(5)	C(2')	O(2')	C(8')	116.0(5)
C(3)	O(3)	C(10)	115.8(5)	C(3')	O(3')	C(10')	116.6(5)
C(2)	C(1)	C(6)	115.1(5)	C(2)	C(1)	C(7)	120.9(5)
C(6)	C(1)	C(7)	61.1(4)	C(2')	C(1')	C(6')	115.8(5)
C(2')	C(1')	C(7')	119.7(5)	C(6')	C(1')	C(7')	59.8(4)
O(2)	C(2)	C(1)	110.0(5)	O(2)	C(2)	C(3)	106.5(4)
C(1)	C(2)	C(3)	113.8(5)	O(2')	C(2')	C(1')	109.4(5)
O(2')	C(2')	C(3')	106.9(5)	C(1')	C(2')	C(3')	111.3(5)
O(3)	C(3)	C(2)	107.5(5)	O(3)	C(3)	C(4)	109.0(5)
C(2)	C(3)	C(4)	111.5(5)	O(3')	C(3')	C(2')	107.8(5)
O(3')	C(3')	C(4')	107.9(4)	C(2')	C(3')	C(4')	112.2(5)
C(3)	C(4)	C(4')	119.3(5)	C(3)	C(4)	C(5)	119.0(5)
C(4')	C(4)	C(5)	121.6(6)	C(3')	C(4')	C(4)	119.1(5)
C(3')	C(4')	C(5')	119.3(6)	C(4)	C(4')	C(5')	121.4(6)
C(4)	C(5)	C(6)	123.8(6)	C(4')	C(5')	C(6')	122.5(6)
C(1)	C(6)	C(5)	116.5(5)	C(1)	C(6)	C(7)	57.6(4)
C(5)	C(6)	C(7)	120.9(5)	C(1')	C(6')	C(5')	116.3(5)
C(1')	C(6')	C(7')	59.1(4)	C(5')	C(6')	C(7')	121.2(6)
Cl(71)	C(7)	Cl(72)	112.5(4)	Cl(71)	C(7)	C(1)	117.3(5)
Cl(71)	C(7)	C(6)	116.3(4)	Cl(72)	C(7)	C(1)	121.2(4)
Cl(72)	C(7)	C(6)	119.2(5)	C(1)	C(7)	C(6)	61.3(4)
Cl(71')	C(7')	Cl(72')	112.3(4)	Cl(71')	C(7')	C(1')	122.3(5)
Cl(71')	C(7')	C(6')	121.3(5)	Cl(72')	C(7')	C(1')	115.3(4)
Cl(72')	C(7')	C(6')	115.8(4)	C(1')	C(7')	C(6')	61.1(4)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
O(2)	C(8)	O(8)	123.3(7)	O(2)	C(8)	C(9)	110.1(7)
O(8)	C(8)	C(9)	126.6(7)	O(2')	C(8')	O(8')	122.9(6)
O(2')	C(8')	C(9')	111.5(6)	O(8')	C(8')	C(9')	125.6(6)
O(3)	C(10)	O(10)	123.5(6)	O(3)	C(10)	C(11)	109.7(7)
O(10)	C(10)	C(11)	126.7(7)	O(3')	C(10')	O(10')	122.4(6)
O(3')	C(10')	C(11')	110.4(6)	O(10')	C(10')	C(11')	127.2(6)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	C(1)	H(1)	111.1	C(6)	C(1)	H(1)	107.0
C(7)	C(1)	H(1)	126.8	C(2')	C(1')	H(1')	104.3
C(6')	C(1')	H(1')	130.3	C(7')	C(1')	H(1')	122.6
O(2)	C(2)	H(2)	108.8	C(1)	C(2)	H(2)	108.8
C(3)	C(2)	H(2)	108.8	O(2')	C(2')	H(2')	109.7
C(1')	C(2')	H(2')	109.7	C(3')	C(2')	H(2')	109.7
O(3)	C(3)	H(3)	109.6	C(2)	C(3)	H(3)	109.6
C(4)	C(3)	H(3)	109.6	O(3')	C(3')	H(3')	109.6
C(2')	C(3')	H(3')	109.6	C(4')	C(3')	H(3')	109.6
C(4)	C(5)	H(5)	118.1	C(6)	C(5)	H(5)	118.1
C(4')	C(5')	H(5')	118.7	C(6')	C(5')	H(5')	118.7
C(1)	C(6)	H(6)	112.4	C(5)	C(6)	H(6)	129.0
C(7)	C(6)	H(6)	96.5	C(1')	C(6')	H(6')	111.5
C(5')	C(6')	H(6')	127.1	C(7')	C(6')	H(6')	101.9
C(8)	C(9)	H(9c)	109.5	C(8)	C(9)	H(9a)	109.5
C(8)	C(9)	H(9b)	109.5	H(9c)	C(9)	H(9a)	109.5
H(9c)	C(9)	H(9b)	109.5	H(9a)	C(9)	H(9b)	109.5
C(8')	C(9')	H(9'a)	109.5	C(8')	C(9')	H(9'b)	109.5
C(8')	C(9')	H(9'c)	109.5	H(9'a)	C(9')	H(9'b)	109.5
H(9'a)	C(9')	H(9'c)	109.5	H(9'b)	C(9')	H(9'c)	109.5
C(10)	C(11)	H(11c)	109.5	C(10)	C(11)	H(11a)	109.5
C(10)	C(11)	H(11b)	109.5	H(11c)	C(11)	H(11a)	109.5
H(11c)	C(11)	H(11b)	109.5	H(11a)	C(11)	H(11b)	109.5
C(10')	C(11')	H(11'a	109.5	C(10')	C(11')	H(11'b	109.5

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(10')	C(11')	H(11'c	109.5	H(11'a	C(11')	H(11'b	109.5
H(11'a	C(11')	H(11'c	109.5	H(11'b	C(11')	H(11'c	109.5

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Cl(71)	C(7)	C(1)	C(2)	149.9(5)	Cl(71)	C(7)	C(1)	C(6)	-106.7(5)
Cl(71)	C(7)	C(6)	C(1)	108.2(5)	Cl(71)	C(7)	C(6)	C(5)	-148.1(5)
Cl(71'	C(7')	C(1')	C(2')	6.4(8)	Cl(71'	C(7')	C(1')	C(6')	110.7(6)
Cl(71'	C(7')	C(6')	C(1')	-112.2(6)	Cl(71'	C(7')	C(6')	C(5')	-8.2(9)
Cl(72)	C(7)	C(1)	C(2)	5.2(9)	Cl(72)	C(7)	C(1)	C(6)	108.6(6)
Cl(72)	C(7)	C(6)	C(1)	-111.7(5)	Cl(72)	C(7)	C(6)	C(5)	-8.0(8)
Cl(72'	C(7')	C(1')	C(2')	148.9(5)	Cl(72'	C(7')	C(1')	C(6')	-106.8(5)
Cl(72'	C(7')	C(6')	C(1')	105.9(5)	Cl(72'	C(7')	C(6')	C(5')	-150.0(5)
O(2)	C(2)	C(1)	C(6)	152.7(5)	O(2)	C(2)	C(1)	C(7)	-137.2(6)
O(2)	C(2)	C(3)	O(3)	-53.4(6)	O(2)	C(2)	C(3)	C(4)	-172.9(5)
O(2')	C(2')	C(1')	C(6')	155.7(5)	O(2')	C(2')	C(1')	C(7')	-135.9(6)
O(2')	C(2')	C(3')	O(3')	-54.1(6)	O(2')	C(2')	C(3')	C(4')	-172.7(4)
O(3)	C(3)	C(2)	C(1)	68.0(6)	O(3)	C(3)	C(4)	C(4')	93.7(6)
O(3)	C(3)	C(4)	C(5)	-83.6(7)	O(3')	C(3')	C(2')	C(1')	65.4(6)
O(3')	C(3')	C(4')	C(4)	89.3(6)	O(3')	C(3')	C(4')	C(5')	-85.8(7)
O(8')	C(8')	O(2')	C(2')	3.9(8)	O(8)	C(8)	O(2)	C(2)	4(1)
O(10)	C(10)	O(3)	C(3)	1(1)	O(10')	C(10')	O(3')	C(3')	2(1)
C(1)	C(2)	O(2)	C(8)	76.2(6)	C(1)	C(2)	C(3)	C(4)	-51.5(7)
C(1)	C(6)	C(5)	C(4)	-20.4(9)	C(1)	C(7)	C(6)	C(5)	103.7(6)
C(1')	C(2')	O(2')	C(8')	74.1(6)	C(1')	C(2')	C(3')	C(4')	-53.3(6)
C(1')	C(6')	C(5')	C(4')	-22.4(9)	C(1')	C(7')	C(6')	C(5')	104.0(6)
C(2)	O(2)	C(8)	C(9)	-175.7(5)	C(2)	C(1)	C(6)	C(5)	1.7(8)
C(2)	C(1)	C(6)	C(7)	113.0(6)	C(2)	C(1)	C(7)	C(6)	-103.5(6)
C(2)	C(3)	O(3)	C(10)	145.2(5)	C(2)	C(3)	C(4)	C(4')	-147.7(5)

Table 7. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(2)	C(3)	C(4)	C(5)	35.0(8)	C(2')	O(2')	C(8')	C(9')	-176.6(5)
C(2')	C(1')	C(6')	C(5')	-1.3(8)	C(2')	C(1')	C(6')	C(7')	110.9(6)
C(2')	C(1')	C(7')	C(6')	-104.3(6)	C(2')	C(3')	O(3')	C(10')	140.3(6)
C(2')	C(3')	C(4')	C(4)	-152.1(5)	C(2')	C(3')	C(4')	C(5')	32.8(8)
C(3)	O(3)	C(10)	C(11)	-176.8(5)	C(3)	C(2)	O(2)	C(8)	-159.9(5)
C(3)	C(2)	C(1)	C(6)	33.3(7)	C(3)	C(2)	C(1)	C(7)	103.3(7)
C(3)	C(4)	C(4')	C(3')	48.1(8)	C(3)	C(4)	C(4')	C(5')	-136.8(6)
C(3)	C(4)	C(5)	C(6)	1(1)	C(3')	O(3')	C(10')	C(11')	-178.2(5)
C(3')	C(2')	O(2')	C(8')	-165.3(5)	C(3')	C(2')	C(1')	C(6')	37.8(7)
C(3')	C(2')	C(1')	C(7')	106.2(6)	C(3')	C(4')	C(4)	C(5)	-134.7(6)
C(3')	C(4')	C(5')	C(6')	6(1)	C(4)	C(3)	O(3)	C(10)	-93.7(6)
C(4)	C(4')	C(5')	C(6')	-168.8(6)	C(4)	C(5)	C(6)	C(7)	-86.9(8)
C(4')	C(3')	O(3')	C(10')	-98.3(6)	C(4')	C(4)	C(5)	C(6)	-176.1(6)
C(4')	C(5')	C(6')	C(7')	-90.7(8)	C(5)	C(4)	C(4')	C(5')	40.3(9)
C(5)	C(6)	C(1)	C(7)	-111.3(6)	C(5')	C(6')	C(1')	C(7')	-112.1(6)

Table 8. Non-bonded Contacts out to 3.60 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
Cl(71)	O(2)	3.248(4)	45501	Cl(72'	O(8)	3.569(6)	54501
O(8')	C(5')	3.164(8)	65501	O(8')	C(11')	3.382(9)	54502
O(8')	C(6')	3.463(7)	65501	O(8')	O(10')	3.563(6)	54502
O(8)	C(11)	3.40(1)	45402	O(8)	C(9')	3.493(9)	2
O(10)	C(6)	3.366(8)	65501	O(10)	C(9)	3.596(9)	54402
O(10')	C(9')	3.475(9)	2	O(10')	C(8')	3.545(8)	2
C(11)	C(11')	3.45(1)	55401				

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	1/2+Y,	-Z